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(54) Title: A METHOD FOR TREATING TENSION–TYPE HEADACHE

(57) Abstract

Tension–type headache is treated by interacting with neuronal transmission in relation to pain in connection with headache in a way which prevents or decreases sensitization of second order nociceptive neurons. In particular, treatment is performed by administration of an effective amount of a substance which prevents or decreases central sensitization. Important examples of such substances are substances which interact with glutamate neurotransmission, such as glutamate receptor antagonists, such as NMDA receptor antagonists, such as MK–801 or Amitriptylline or Imipramine or Desipramine or Mirtazaprine or Venlafaxine. Other examples are substances which interact with nitric oxide, such as nitric oxide synthase (NOS) inhibitors, such as L–NMMA or L–NAME or L–NIO or L–NNA. According to a broader aspect of the invention tension–type headache is treated by administration of substances which are effective in preventing or decreasing pain in connection with tension–type headache, such as the substances mentioned above. An additional aspect of the invention relates to treatment of tension–type headache by administration of substances which substantially inhibit the activity of nitric oxide synthase (NOS), such as NOS inhibitors, such as L–NMMA or L–NAME or L–NIO or L–NNA.

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A method for treating tension-type headache

## FIELD OF THE INVENTION

The present invention relates to a method of treatment of tension-type headache in a human in need of such treatment. In particular, the invention relates to a method of treatment of tension-type headache comprising the administration of a substance or substances effective for the prevention or normalization of an otherwise qualitatively altered stimulus-response function in connection with nociception.

## GENERAL BACKGROUND

### Types of clearly defined headache disorders.

Previously, headache disorders were not clearly distinguished and it was widely believed that they formed part of a continuum and were strongly related. In 1988, The International Headache Society, (IHS) via its ad hoc committee on classification published a document entitled Classification and Diagnostic Criteria for Headache Disorders, Cranial Neuralgias and Facial Pain (Classification and Diagnostic Criteria for Headache Disorders, 1988). A new entity was here defined by name of tension-type headache. This entity was practically the same as conditions previously called tension headache, muscle contraction headache, psycho-myogenic headache and idiopathic headache. The IHS classification also defined a number of other specific headache diseases. Today it therefore gives no meaning to talk about headache in general. It would be the same as to discuss bellyache and chest pain without specifying its type and etiology. Due to the development in diagnostic accuracy research results obtained before 1988 have uncertain validity.

Tension-type headache was subdivided by the IHS Classification Committee into an episodic form occurring less than half of all days and a chronic form occurring half of all days or more. Furthermore, both of these divisions were further subdivided into a form with disorder of pericranial muscle and a form without such disorder. It is thus crucial that research and patents specify which of the subforms are included.

Before the entity of tension-type headache was created, it was widely believed that this kind of headache was caused by muscle ischemia, a concept later disproven by the present inventors (Langemark et al. 1990). The term tension-type headache was created in order to indicate that experts disagreed with the notion of tension-type headache being simply a kind of muscle pain. In fact, the term idiopathic headache was suggested. There is only a moderate co-morbidity with neck pain and low back pain in sufferers of tension-type headache. Furthermore, Electromyography (EMG)-measurements have failed to detect an increase of muscle contraction

sufficient to cause pain on a purely mechanical basis in tension-type headache patients whereas central factors such as depression and anxiety have been attributed a significant role. Finally, a genetic factor has recently been shown to be involved in tension-type headache (Østergaard et al. 1996). From the point of view of mechanisms and definition tension-type headache is thus a specific entity which may or may not share mechanisms with muscle pain in the head and in other parts of the body. The classification and diagnostic criteria for tension-type headache are shown in Tables I and II.

**Table I.** Classification of headache disorders, cranial neuralgias, and facial pain (Headache Classification Committee 1988).

1. Migraine
2. Tension-type headache
3. Cluster headache and chronic paroxysmal hemicrania
4. Miscellaneous headaches unassociated with structural lesion
5. Headache associated with head trauma
6. Headache associated with vascular disorders
7. Headache associated with non-vascular intra-cranial disorder
8. Headache associated with substances or their withdrawal
9. Headache associated with noncephalic infection
10. Headache associated with metabolic disorder
11. Headache or facial pain associated with disorder of cranium, neck, eyes, nose, sinuses, teeth, mouth or other facial or cranial structures

12 Cranial neuralgias, nerve trunk pain and deafferentation pain

13. Headache not classifiable

**Table II** Diagnostic criteria for episodic and chronic tension-type headache (Headache Classification Committee 1988)

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II.1. Episodic tension-type headache

A. At least 10 previous headache episodes fulfilling criteria B-D listed below.
   Number of days with such headache < 180/year (<15/month)

B. Headache lasting from 30 minutes to 7 days

C. At least 2 of the following pain characteristics:
   1. Pressing/tightening quality
   2. Mild or moderate severity (may inhibit, but does not prohibit activities)
   3. Bilateral location
   4. No aggravation by walking stairs or similar routine physical activity

D. Both of the following:
   1. No nausea or vomiting (anorexia may occur)
   2. Photophobia and phonophobia are absent, or one but not the other is present

E. At least one of the following:
   1. History, physical and neurological examinations do not suggest one of the disorders listed in groups 5-11
   2. History and/or physical and/or neurological examinations do suggest such disorders, but they are ruled out by appropriate investigations
   3. Such disorders are present, but tension-type headache does not occur for the first time in close temporal relation to the disorder

II.2. Chronic tension-type headache

A. Average headache frequency 15 days/month (180 days/year) for 6 months fulfilling criteria B-D listed below

B. At least 2 of the following pain characteristics:
   1. Pressing/tightening quality
   2. Mild or moderate severity (may inhibit, but does not prohibit activities)
   3. Bilateral location
   4. No aggravation by walking stairs or similar routine physical activity

C. Both of the following:
   1. No vomiting
   2. No more than one of the following:
      Nausea, photophobia or phonophobia

D. At least one of the following:
   1. History, physical and neurological examinations do not suggest one of the disorders listed in groups 5-11
   2. History and/or physical and/or neurological examinations do suggest such disorders, but they are ruled out by appropriate investigations
   3. Such disorders are present, but tension-type headache does not occur for the first time in close temporal relation to the disorder

Epidemiological studies done by the inventors have shown that chronic tension-type headache affects three per cent of the population at any given time, the lifetime prevalence being as high as six per cent (Rasmussen et al. 1991). Severe episodic tension-type headache defined as persons having headache twice a week or more occurs in approximately ten per cent of the population. Thus, tension-type headache is a serious problem with significant socio-economic implications, involving enormous loss of workdays and quality of life.

**Previous findings in general pain physiology and pain pharmacology**

The possible pathogenic mechanisms of tension-type headache have previously been studied and discussed by Langemark et al. (Langemark et al. 1987, 1988, 1989) and by the group of Jean Schoenen (Schoenen et al. 1987, 1991a, b). The latter group have mainly focused on electrophysiological recordings as electromyography, and the jaw opening reflex as reflected by the so-called exteroceptive silent period (ES2) (Schoenen et al. 1987). On the basis of shortened ES2 periods in patients with chronic tension-type headache compared to healthy controls a limbic dysfunction was suggested, but these results have later been disproven by more systematic investigations (Bendtsen et al. 1996a, Lipchik et al 1996, Zwart and Sand, 1996). Schoenen and other groups have also studied mechanical pain thresholds on the extremities as

well as in the cranial region and decreased mechanical pain thresholds in severely affected patients with chronic tension-type headache were reported (Schoenen et al. 1991a, Langemark et al. 1989), whereas patients with the episodic form of tension-type headache are reported to have normal thresholds compared to healthy controls (Hatch et al. 1992, Goebel et al. 1992, Jensen et al. 1993b). These authors suggested that central mechanisms may be involved in the chronic subform and that the peripheral mechanisms played a role in the episodic form, but provided no further clues or arguments about the underlying mechanisms. One more recent congress presentation and two scientific papers by the present inventors have focused on the sensory mechanisms in tension-type headache as decreased thresholds and tolerances were found in and outside the head of patients with chronic tension-type headache indicating a generally increased sensitivity to noxious and innocuous stimuli (Bendtsen et al. 1995b, 1996b and 1996c). Similarly a congress report and a scientific paper present data from patients studied during and outside a spontaneous tension-type headache episode (Jensen et al. 1995a and 1995b). Muscle tenderness was increased during the headache episode, whereas mechanical pain thresholds remained unchanged and thermal pain tolerance decreased. Furthermore, two recent congress presentations and a scientific paper presented data from a study of 28 patients with episodic tension-type headache and 28 patients with chronic tension-type headache with specific focus on muscular factors (Jensen et al. 1996a, b, c, Example 5). The results indicate that prolonged nociceptive stimuli from the pericranial myofascial tissue sensitize the central nervous system and thereby lead to an increased general pain sensitivity. It was concluded that a peripheral sensitization may be one of the primary sources of pain and that central sensitization may contribute to and maintain the pain in chronic tension-type headache. However, these data did not provide any further clues for more specific localizations of the sensitization, could not lead to a precise experimental model and finally did not lead to guidance for specific treatment of tension-type headache.

**Peripheral induction of central sensitization**

One of the most exciting developments in pain research over the past decades has been the recognition that the response generated by the somatosensory system to a defined input is not fixed or static. In particular, the increased knowledge on central sensitization, i.e. increased excitability of neurons in the central nervous system, has been a major breakthrough in the understanding of chronic pain. In 1983 Woolf and colleagues (Woolf 1983) demonstrated for the first time that a prolonged noxious input from the periphery is capable of sensitizing spinal dorsal horn neurones. It has later been demonstrated that the central sensitization is induced by repetitive C-fibre, but not A-fibre, input (Yaksh and Malmberg 1994). In the sensitized state, a low-intensity stimulus can generate pain, the phenomenon of allodynia. The low-intensity stimulus is mediated via low-threshold afferents, A-β-fibres, which do not normally mediate

pain, and it has been suggested that the major cause of increased pain sensitivity in the chronic pain condition is an abnormal response to A-β-sensory input (Woolf and Doubell 1994). The original findings by Woolf and colleagues on spinal dorsal horn sensitization have later been confirmed by numerous independent laboratories (Mense 1993), and a similar sensitization of trigeminal brainstem nociceptive neurons following stimulation of craniofacial muscle afferents has been reported by Hu et al. (Hu et al. 1992). While central sensitization may be of relevance in many different chronic pain conditions it is particular likely in muscle pain, because input from muscle nociceptors is more effective in inducing prolonged changes in the behaviour of dorsal horn neurons than is input from cutaneous nociceptors (Wall and Woolf 1984).

## SUMMARY OF THE INVENTION

The inventors of the present invention have discovered that patients suffering from increased myofascial pain in connection with tension-type headache display a qualitatively altered stimulus/response function in connection with nociception when tender trapezius muscle is palpated. This discovery and analysis of curves representing the stimulus/response function strongly suggest that the alteration is primarily caused by central sensitization of second order neurons. The present inventors were then able to devise, for the first time, an effective treatment of tension-type headache, which comprises interacting with neuronal transmission connected with nociception so as to substantially prevent or normalize an otherwise qualitatively altered stimulus/response function in connection with pain perception.

A better understanding of the principle of the invention can be derived from the detailed description of the scientific background in the scientific section below.

## SCIENTIFIC SECTION

### Previous findings in general pain physiology and pain pharmacology and previous findings in tension-type headache.

Pain physiology and pain pharmacology have mostly been elucidated in animal studies. There are, however, no animal models with any proven validity in tension-type headache. Furthermore, these animal experimental studies are done in anaesthetized animals while the sensation of pain by definition can only occur in awake beings. Most of the experiments are also of an acute nature stimulating for milliseconds and recording responses for seconds, minutes or hours and are therefore of uncertain validity for chronic tension-type headache. Finally, only few studies have been done on myofascial tissues projecting via the trigeminal nerve while the huge body of knowledge otherwise available deals with mechanisms of the spinal cord. None of the

experimental animal studies mention any form of headache, neither do they suggest that the results of these studies may be utilized for the treatment of tension-type headache.

However, after the crucial findings leading to the present invention were made, it is clear that the implications of the findings in relation to general pain physiology can also be utilized in relation to tension-type headache.

With respect to medicinal treatment of tension-type headache, the prior art mentions a varity of substances. The substance Flupirtin, which is suggested to work as an NMDA glutamate receptor antagonist (Schwartz et al. 1981), has been suggested for use in the treatment of chronic or episodic tension-type headache, as disclosed in EP 0 659 410 A2, and according to Wörz et al., 1996, it has shown positive effects. However, in these documents the substance is described as a muscle relaxant, and the mechanism by which it is proposed to exert its effect in the treatment of various conditions, including tension-type headache, is by lowering muscle tension. Thus, as opposed to the present inventors, the prior art understands and explains tension-type headache as a condition directly and primarily caused by muscle tension. WO 96/32386 concerns arylglycinamide derivatives which are antagonists of neurokinins, and these compounds are broadly claimed for use in the treatment of a wide variety of conditions in which neurokinins are supposed to be implicated. Tension-type headache is mentioned as such a condition, but there is no indication of what the mechanism of neurokinin involvement might be. WO 96/29326 discloses 3-benzylamino-2-phenylpiperidines and states that they are neurokinin antagonists working through NK1 receptors and are suggested for treatment of pain conditions in general, including tension-type headache. No exact mechanism is described. For all the above-mentioned prior art documents, it can be said that the concept of central sensitization in relation to tension-type headache, as introduced by the present inventors, is not described or contemplated at all. Indeed, the prior art does not appear to be concerned with the underlying physiological mechanisms of tension-type headache, but seems to reflect presently held notions of pain physiology in general.

In connection with the present invention, the term "3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326" should be taken to mean a compound as defined in any of claims 1-6 of WO 96/29326, and the term "arylglycinamide derivative as disclosed in WO 96/32386" means a compound as defined in any of claims 1-17 of WO 96/32386.

**Novel experimental evidence for neuronal sensitization in tension-type headache.**

As discussed, previous studies in tension-type headache have in general terms indicated that there may be sensitization of muscle and nociceptive afferents and also in a non-specific way

have suggested some kind of central sensitization. Whether one or the other kind of sensitization is the more important or whether indeed they both co-exist has not been clear. Recent series of experiments by the present inventors have now clearly shown that tension-type headache is indeed much more complicated than previously anticipated; thus neither the phenomenon of peripheral sensitization nor that of unspecific central sensitization does in isolation explain the condition. The studies of the present inventors have demonstrated that mechanical force due to contraction of chewing muscles may induce peripheral sensitization in chewing muscles and that this peripheral sensitization is an important factor which may or may not induce headache (Jensen and Olesen 1996). Whether this happens depends on the response of the central nervous system. Further experiments have shown for the first time that a qualitatively altered pain perception related to sensitization of second order nociceptive neurons is chronically present in subjects with tension-type headache (Bendtsen et al. 1996c). This is believed to be far the most important abnormality in tension-type headache. Thirdly, recent studies by the present inventors have demonstrated that in addition to sensitization of second order nociceptive neurons, there is also a component of a more unspecific sensitization of pain pathways at higher levels of the central nervous system (Bendtsen et al. 1996b). While sensitization of second order neurons is believed to be a segmental (located only in those segments of the spinal cord/trigeminal nucleus which receive afference from myofascial tissues), the sensitization of higher centers is of a general nature and results in increased pain sensitivity all over the body. On the basis of the combined findings of the inventors, a novel and rather complex model of the mechanisms of tension-type headache has been developed, as depicted in fig. 1. In the following the model is described in details and its significant implications for devising successful future drug treatment of tension-type headache are discussed.

The model is illustrated in Fig. 1, in which the abbreviations have the following meaning:

| | |
|---|---|
| V: | Trigeminal nerve, |
| C2, C3: | Second and third cervical segment of the spinal cord, |
| PAG: | Periaquaductal grey, |
| DRN: | Dorsal raphe nuclei, |
| on-cells: | cells in ventromedial medulla, which activate pain pathways, for instance by reducing the threshold in the tail flick test. |
| C, Aδ, Aβ: | Fibers of the C, Aδ, and Aβ type |

**Model for the development of tension-type headache involving neuronal sensitization.**

The main circuitry in Fig. 1 is the following:
Voluntary muscle activity is initiated by the supplementary motor area. This activates the motor cortex which again activates the motor nucleus of the trigeminal nerve and anterior horn cells of the C2 and C3 segments of the spinal cord causing contraction of chewing and neck muscles. Simultaneously with the activation of motor cortex, the supplementary motor area also activates the antinociceptive system. Therefore normal muscle activity, even when vigorous, is not normally perceived as painful. Another way of activating the motor pathways is via the limbic system which is concerned with emotions. When this system is activated, as in states of anxiety and stress, it is envisaged that the motor cortex and the pain facilitatory system are activated simultaneously. Thus, emotionally induced involuntary muscle contraction usually induces myofascial tenderness and pain. Both voluntary and emotionally triggered muscle contraction via mechanical stress and perhaps neurogenic inflammation increase afferent input from myofascial tissues via C-fibers, A-δ-fibers and A-β-fibers. C-fiber input is responsible for slow pain and, when prolonged, causes the so-called wind-up phenomenon in second order neurons located in the nucleus of the trigeminal tract and in segments C2 and C3 of the dorsal horn of the spinal cord. Wind-up is associated with increased sensitivity of second order neurons and an increase of their receptive fields. Furthermore, input via A-β-fibers becomes painful which is called allodynia. Input from the periphery in a state of wind-up causes a more intense pain than normally. With repeated or chronic micro traumatic or inflammatory reactions in myofascial tissues peripheral nociceptores, primarily projecting via C-fibers, become sensitized. Substances involved in peripheral sensitization include the potassium ion, bradykinin, histamine, ATP, neurotrophins and possibly other growth factors (Meyer et al. 1994).

**Synaptic mechanisms in the spinal dorsal horn/trigeminal nucleus involved in central sensitization**

How does repetitive C-fibre input to the spinal dorsal horn result in abnormal responses to normal Aβ-fibre inputs, i.e. in central sensitization? The most likely answer is that C-fibre released neurotransmitters increase the excitability of dorsal horn neurons, so that previously ineffective Aβ-fibre inputs to nociceptive dorsal horn neurons become effective (Woolf and Thompson 1991). Several neurotransmitters are known to be involved in nociceptive transmission from C-fibre afferents to second order neurons in the spinal dorsal horn. These neurotransmitters can largely be divided into gases, into peptides, which are chains of amino acids, or into excitatory or inhibitory amino acids, which are chemically single amino acids and into excitatory or inhibitory amines.

*Gases*

The freely diffusible gas nitric oxide (NO) is probably released from C-fibres and acts after binding to the enzyme guanylate cyclase in postsynaptic neurons. However, even though NO is considered of major importance in central sensitization, its exact role as a neurotransmitter is not yet clarified (Meller and Gebhart 1993).

*Neurokinins*

Neurokinins are a family of related peptides, including substance P, neurokinin A, neurokinin B and bradykinin which are known to be released from C-fibres. Currently there are three known subclasses of receptors for these peptides: neurokinin-1 ($NK_1$), $NK_2$ and $NK_3$ receptors.

*PACAP*

PACAP is expressed in abundant amounts in dorsal horn neurons and is believed to play a significant role in pain transmission or the modulation of pain transmission.

*Calcitonin gene-related peptide (CGRP)*

The exact role of this peptide in pain transmission is not known because of lack of selective receptor antagonists. However, CGRP probably protracts the breakdown of substance P in the synaptic cleft, thereby adding to the level of excitability of the spinal cord (Dickenson 1996).

*Other peptides*

Several other peptides such as somatostatin, neuropeptide Y and galanin may be important, but their exact role in central sensitization is not yet known.

*Excitatory amino acids*

It now appears that the excitatory amino acid glutamate plays a dominant role in the development of central sensitization. Glutamate is used by most neurons in the brain and spinal cord as their major excitatory transmitter. The actions of glutamate are mediated by 4 different receptor classes: the N-methyl-D-aspartate (NMDA), the α-amino-3-hydroxy-5-methyl-4-isoxazolyl-propionic acid (AMPA), the kainate receptors, and the metabotropic receptors. Of these receptors, especially the NMDA receptors are considered to be of crucial importance in central sensitization (Coderre et al. 1993).

*Adenosine*

The central terminals of primary afferent fibres do express adenosine receptors (Levine and Taiwo 1994). Via these receptors, adenosine can inhibit voltage-gated calcium channels via activation of a G-protein resulting in an inhibition of transmitter release from the primary afferent neuron (Rang et al. 1994). Adenosine agonists may also act to inhibit the firing of wide-

dynamic neurons, probably through an increase in potassium conductance. Furthermore, adenosine has been reported to block the release of glutamate (Yaksh and Malmberg 1994). In support of these findings intrathecal adenosine has been shown to increase the nociceptive threshold (Yaksh and Malmberg 1994). Adenosine does also play a role in the peripheral tissues. In the primary afferent nociceptor adenosine acting at the $A_1$-receptor inhibit hyperalgesia, while adenosine acting at the $A_2$-receptor produces hyperalgesia via elevation of intracellular cAMP (Levine and Taiwo 1994).

*Gamma amino butyric acid (GABA)*

GABA is an important inhibitory transmitter in the central nervous system, and it has been suggested that the encoding of low-threshold mechanical stimuli as innocuous depends completely upon the presence of a tonic activation of intrinsic glycine and/or GABAergic neurons (Yaksh and Malmberg 1994). Furthermore, it has been demonstrated that the administration of GABA antagonists can produce allodynia (Woolf 1994). $GABA_B$ agonists may act to inhibit the firing of wide-dynamic neurons, probably through an increase in potassium conductance (Yaksh and Malmberg 1994) and GABA may also reduce the amount of transmitter release from the central terminals of primary afferent fibres by opening of chloride channels (Rang et al. 1994).

*5-hydroxytryptamine (5-HT)*

5-HT is a very important transmitter in the modulation of pain. While 5-HT has both analgesic and algesic properties, it acts mainly as an inhibitory pain transmitter in the central nervous system (Roberts 1992). Thus, when 5-HT is applied directly to the spinal cord, it produces analgesia (Fields and Basbaum 1994). The antinociceptive effects of 5-HT are mediated via many different 5-HT receptor subtypes. Thus, it is known that both the $5\text{-HT}_1$, $5\text{-HT}_2$ and $5\text{-HT}_3$ receptors are involved in antinociception (Fields and Basbaum 1994).

*Norepinephrine (NE)*

Like 5-HT, also norepinephrine (NE) plays an important role as an endogenous antinociceptive transmitter. In general, noradrenergic controls are mediated at the spinal level by the action at the $\alpha$-2-adrenergic receptor (Fields and Basbaum 1994). The $\alpha$-2-agonist clonidine has been shown to block the release of transmitters and peptides in primary afferent terminals by presynaptic action, and it is most likely that the analgesic effects of the tricyclic antidepressants partly depend on their inhibition of norepinephrine re-uptake (Boivie 1994).

**Intracellular mechanisms in the spinal dorsal horn/trigeminal nucleus involved in central sensitization.**

Why are the NMDA receptors considered so important? The actions of many receptors on neuronal excitability are via opening or closing of ion channels. The ion channel for the NMDA receptors allows vast amounts of calcium into the neuron, so much that the resultant increase in excitability exceeds that produced by all other receptors (Dickenson 1996). The increase in intracellular calcium initiates a cascade of biochemical events. Thus, calcium activates a calmodulin-sensitive site on NO synthase, which results in the production of NO. NO may thereafter act via at least three different mechanisms: 1) it may act in the neuron where it is produced, e.g. by increasing cyclic guanylate mono phososphate (cGMP) levels which again will activate protein kinases or by inducing the expression of immediate early genes. The protein kinases and the protein products of immediate early genes may then act as third messengers and control the expression of other genes involved in the synthesis of growth factors, channel proteins, peptides and enzymes; 2) it may act as a retrograde transmitter by diffusion to the presynaptic neuron where it modulates excitability and enhances synaptic connections; and 3) it may diffuse to adjacent neurons, e.g. interneurons (Meller and Gebhart 1993). Another important result of increased intracellular calcium is the activation of phospholipase $A_2$, leading to increases in intracellular arachidonic acid and the subsequent formation of cyclooxygenase and lipooxygenase products. Prostaglandins have been shown to increase calcium conductance on dorsal root ganglion cells and to increase the secretion of primary afferent peptides such as substance P (Yaksh and Malmberg 1994). Activation of the NMDA receptors thus has dramatic consequences and the receptors are therefore usually blocked, such that they do not participate in normal transmission. This channel block, which is mediated by physiological levels of $Mg^{2+}$ ions, can only be removed by sufficient repeated depolarization of the membrane. It is suspected that the neurokinins co-released with glutamate from C-fibres contribute to the removal of $Mg^{2+}$ ions. This important action of the neurokinins is probably mediated via $NK_1$ and $NK_2$ receptors (Dickenson 1996). Also the protein kinases activated by NO will feed back on the NMDA receptors, causing phosphorylation and partial removal of the $Mg^{2+}$ channel blockade (Woolf 1996). Other glutamate receptors are probably also involved in central sensitization, but the exact mechanisms are not yet known.

**Altered pain perception after central sensitization**

The increased excitability of neurons in the spinal dorsal horn/trigeminal nucleus has dramatic consequences for the pain perception in the individual patient. In the sensitized state, pain can be generated by low-threshold Aβ-fibres (allodynia) (Torebjörk et al. 1992), the response to activation of high-threshold afferents is exaggerated (hyperalgesia) (Woolf 1994), and since the

receptive field of the dorsal horn neuron is increased, the central sensitization will also be manifest as a spread of hypersensitivity to uninjured sites (secondary hyperalgesia) (Torebjörk et al. 1992).

**Central sensitization in the brain**

When noxious input is received in the nucleus of the trigeminal tract, its further transmission to the thalamus and sensory cortex depends on the intensity of the input and on the balance between pain inhibiting and pain facilitating descending systems originating from the brain stem. When the pain inhibiting system is activated, it decreases the likelihood that incoming stimuli are being transmitted to the thalamus and, alternatively, when the facilitatory system is activated, it increases the likelihood of this event. From the thalamus, nociception is projected further to the sensory cortex. Via unknown mechanisms pain causes a reflex increase in muscle tone. It is envisaged that this response to pain is mediated via the limbic system because pain and anxiety are closely interrelated. There is also a cross-talk between nociception and motor activity at the level of the trigeminal nucleus/spinal cord. Finally, pain activates the sympathetic system causing release of noradrenaline. This again is responsible for an increased pain sensation, so-called sympathetically aggravated or maintained pain.

**Detailed model for the progression of tension-type headache**

The progression of episodic tension-type headache into chronic tension-type headache often takes several years and happens only in a minority of episodic tension-type headache sufferers. A genetic disposition (Østergaard et al. 1996) as well as several environmental factors seem to be involved in the development of chronicity. Despite the fact that the progression is continuous, it is best illustrated by a number of scenarios.

*Scenario 1:* Mild and moderate muscle contraction in normals. Voluntary muscle contraction in relation to normal functions such as chewing or head holding is initiated from the supplementary motor cortex. This is probably associated with only a minor increase in nociception from myofascial tissues and no wind-up in non-headache sufferers. Simultaneously the antinociceptive system is activated such that no sensation of pain occurs.

*Scenario 2:* Forceful and/or long-lasting muscle activity in normals. With particularly vigorous muscle activity and especially when it is very protracted, the strain on myofascial tissues may be such that nociception is rather marked and tenderness and local pain may occur, but it is rapidly controlled by local reparative mechanisms in myofascial tissues and a continuously active

antinociceptive system. Tenderness without spontaneous pain on the day after exercise may be a result of this balance or may be a purely local phenomenon.

*Scenario 3:* Involuntary muscle activity induced by the limbic system in normals: In contrast to activation initiated by the supplementary motor area, muscle contraction initiated by the limbic system is not associated with an increased antinociceptive activity. On the contrary it is proposed to be associated with increased activity in the pain facilitatory system. An alternative is a decrease in the activity of the antinociceptive system, but this is unlikely because this system is normally not tonically active. Limbic initiated muscle activity therefore causes pain even with moderate degrees of contraction and also with relatively short-lasting contractions. However, in normals the drive from the limbic system is short lasting and so are the mild changes in myofascial tissues induced by the motor activity. The headache is therefore self limiting.

*Scenario 4:* Voluntary contraction in patients with severe episodic - and chronic but not daily tension-type headache. In most of these individuals voluntary muscle activity will be painful. In part this is due to permanent sensitization of second order neurons in the nucleus of the trigeminal tract, in part it is due to the fact (Jensen and Olesen 1996) that the antinociceptive system is not activated as normally. Contraction therefore aggravates tenderness and causes pain from the myofascial structures (Jensen and Olesen 1996) The process of reverting the system back to normal may be more or less effective. This variable duration of the initiating stimulus accounts for the variable duration of the headache.

*Scenario 5:* Severe (daily) chronic tension-type headache.
In severe chronic tension-type headache there is a state of chronic sensitization in myofascial tissues and in central pain pathways both at the second order neurons and at higher centers. There is a minor constant elevation of EMG signal from cranial muscles. In addition, the most severe cases also have a more diffuse sensitization revealed in decreased pain thresholds throughout the body (Bendtsen et al. 1996b). Chronically increased muscle activity maintains a state of chronic peripheral sensitization which again maintains a state of chronic sensitization in the second order neurons in the nucleus of the trigeminal tract (Bendtsen et al. 1996c). This causes steady inflow of nociceptive signals to the thalamus and the perception of chronic pain by the sensory cortex. This again activates the limbic system and stimulates tonic involuntary muscle activity. In this situation of chronic pain there is probably also activation of the sympathetic nervous system adding a component of sympathetically mediated pain to the whole picture. On top of this chronic situation of sustained pain, it is easy to see how additional strain would result in increased and prolonged pain. A further increase in muscle activity would for instance in the sensitized peripheral myofascial tissues lead to a stronger than normal nociceptive input to the already sensitized nucleus of the trigeminal tract which would project to

already sensitized hemispheric pain centers. A vicious circle has been set up and it may become permanent due to changes in gene transcription and consequent structural changes in neurons and synapses.

**Rationale for the novel strategy according to the invention for the treatment of tension-type headache**

Previous treatments have primarily been directed towards reducing muscle contraction i.e. biofeedback treatment, physiotherapy, dental treatment, exercises and muscle relaxants. All of these treatments have had limited or no success. It follows from the model according to the present inventors that therapeutic intervention should be directed primarily towards the afferent system and above all against sensitization of second order neurons in the nucleus of the trigeminal tract and upper cervical segments. Furthermore, it follows that while intervention using peripherally acting analgesics or other measures which reduce peripheral nociceptive input is sufficient in episodic tension-type headache, this is not so for severe episodic and chronic tension-type headache, where sensitization of second order neurons occurs. In these patients, desensitization of these neurons should be the major target for drug intervention. It may, however, be difficult to desensitize these neurons in face of an ongoing vigorous input from the periphery. Therefore, drugs which reduce peripheral sensitization may be needed in addition to the drugs which desensitize second order nociceptive neurons, or drugs working at both levels may be needed. Preferably, treatment should be given early enough to prevent sensitization of second order neurons. Alternatively, if marked sensitization at the cortical level occurs, the individual being hypersensitive to painful stimuli all over the body, it may not be enough to intervene against the sensitization of second order neurons. For such patients intervention against cortical sensitization is recommended as an additional measure.

**The novel therapeutic principle according to the invention for treatment of tension-type headache**

According to the present invention, several means of intervening against tension-type headache can be envisaged, depending on the level according to the above, at which the intervention is aimed. In either case, be it in the periphery, the second order neurons of the sensory trigeminal nucleus or the cortex, the intervention must target the transmission of nerve impulses. A number of different transmitter substances are involved in this transmission at each level. Thus, the invention, in some of its aspects, relate to the following therapeutic principles in tension-type headache of the chronic type and of the severe episodic type defined as having headaches ten or more days per month:

Administration of drugs which counteract sensitization of second order nociceptive neurons located in the nucleus of the descending tract of the trigeminal nerve and in the C2 and C3 segments of the dorsal cervical horn of the spinal cord. These are defined as drugs which normalize the stimulus response function to pressure on the pericranial muscles.

Administration of drugs which reduce supraspinal pain sensitization to a normal level. These are drugs which normalize the response of pressure pain thresholds in the temporal region to tooth clenching and drugs which normalize pain thresholds in hand.

Administration of drugs which reduce peripheral sensitization defined as drugs which prevent the development of abnormal tenderness due to tooth clenching.

Administration of drugs which normalize the pain response to intra muscular infusion of bradykinin, 5-HT, histamine, prostaglandines and/or nitroglycerine.

Administration of drugs which normalize local pressure pain threshold over myofascial tissues of the head.

Administration of drugs which have more than one of the above effects.

Administration of drugs which in a panel of test patients with tension-type headache have one of the above effects described one by one.

When targeting the transmission of nerve impulses according to the invented model, it is preferred to interact with the following substances relating to neurotransmission in connection with pain:

Glutamate
Substance P
Nitric oxide
GABA

It is particularly preferred to:

Antagonize the effect of glutamic acid
Antagonize the effect of substance P
Antagonize the effect of nitric oxide
Stimulate the effect of GABA.

More specifically, it is preferred to use:

NMDA receptor antagonists
$NK_1$ receptor antagonists
Inhibitors of neuronal nitric oxide synthase (NOS)
GABA A and GABA B receptor agonists

**Counteraction of central sensitization of second order neurons**

In order to counteract central sensitization of second order neurons of the sensory trigeminal nucleus/dorsal horn, it will be advantageous to cause a decrease in neuronal transmission involving the pathways utilizing e.g. the transmitter substances glutamate, nitric oxide, and the neurokinins (bradykinin, neurokinin A, neurokinin B). Also, it will be of interest to counteract the action of second messengers such as guanylate cyclase, cGMP as well as any further steps in the action of cGMP in second order sensory neurons receiving nociceptive input from the head and neck.

**Prevention of central sensitization of second order neurons**

In order to prevent the occurrence of central sensitization of second order neurons of the sensory trigeminal nucleus/dorsal horn, it will be advantageous to normalize neuronal transmission in the peripheral and/or central nervous system involving transmitter substances such as glutamate, GABA, adenosine, substance P, nitric oxide, the neurokinins (bradykinin, neurokinin A, neurokinin B), neurotrophins and histamine. While it might have seemed advantageous to use $5\text{-}HT_{1D}$ receptor agonists because they stabilize presynaptic nociceptive terminals, studies by the inventors have shown that a compound of this class (sumatriptan) is not effective to a clinically relevant extent in tension-type headache although it is highly effective in migraine (Brennum et al. 1992, 1996). Counteracting excitatory 5-HT receptors, such as $5\text{-}HT_2$ and $5\text{-}HT_3$ localized on second order neurons, however, are contemplated to be effective in the treatment of tension-type headache in accordance with the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

On the basis of their experimental discoveries and analyses, the present inventors have devised, for the first time, a strategy for the treatment of tension type headache. Up to now, there has not been any effective treatment available for tension type headache, which has been a very serious problem in view of the very high prevalence of tension-type headache.

The present invention relates to a method of treatment of tension-type headache in a person in need of such treatment, the method comprising interacting with neuronal transmission connected with pain perception so as to obtain a substantial prevention or normalization of an otherwise qualitatively altered stimulus-response function in connection with nociception.

The assessment of the attainment of a substantial normalization of an otherwise qualitatively altered stimulus-response function in connection with nociception can suitably be made by palpation of trapezius muscle and recording of the degree of pain corresponding to the intensity of palpation. When a curve representing the stimulus/response function in connection with nociception, in double logarithmic representation, has become substantially linear, a substantial normalization of the qualitative stimulus/response function has been obtained, cf Example 1 herein.

The interaction with neuronal transmission connected with pain perception will normally be interaction with neuronal transmission connected with second order nociceptive neurons. This interaction will normally involve prevention of sensitization by way of a reduction of C-fiber input to the second order nociceptive neurons or reversal of an already established sensitization of second order nociceptive neurons.

By the term "palpation" is meant the act of applying, with the fingers, pressure to the surface of the body for the purpose of determining the amount of pain elicited in the underlying tissue by said pressure intensity.

In the present context, the term "qualitatively altered stimulus/response function" in connection with nociception means that the function describing the amount of pain elicited by a given pressure intensity, sensed by a person being palpated, has changed in shape from being positively accelerating to being substantially linear, cf Example 1.

By the term "tender muscle" is meant a muscle in which pain is elicited by palpation with a clinically relevant pressure.

In the present context, by the term "central sensitization" is meant that second order nociceptive neurons residing in the central nervous system are rendered more sensitive than normally to incoming synaptic stimuli. At the occurrence of central sensitization such stimuli will elicit excitation of the said central neurons at stimulation below the normal threshold for excitation; thus, central neurons possess an increased excitability.

In the present context, myofascial pain relates to pain in the myofascial tissue, by which is meant muscular structures, tendons and tendon insertions related to the pericranial and cervical region.

In the context of the present invention second order nociceptive neurons are neurons located in the nucleus of the trigeminal tract and of C2 and C3 segments of medullary dorsal horns, said neurons being involved in the processing of nociceptive stimuli.

By the term "C-fibers" is meant a class unmyelinated nociceptive fibers terminating on neurons in the nucleus of the trigeminal tract/dorsal horn of the spinal cord.

The interaction with neuronal transmission connected with pain perception so as to obtain a substantial prevention or normalization of an otherwise qualitatively altered stimulus-response function in connection with nociception is preferably performed by administering an effective amount of a substance which prevents or normalizes an otherwise qualitatively altered stimulus-response function in connection with nociception.

In the present context, a substance which prevents or normalizes an otherwise qualitatively altered stimulus-response function in connection with nociception is a substance which, when administered to a group of at least 20 patients suffering from tension type headache as defined above, will cause the curve representing the stimulus/response function in connection with nociception to become substantially linear when represented double logarithmically in at least 10 of the patients, preferably at least 12 of the patients, more preferably in at least 14 of the patients.

A number of substances and classes of substances which interact with neuronal transmission to exert this function are known, confer the detailed discussion thereof in the following.

In accordance with what is explained above, another way of expressing the treatment according to the invention is by reference to pain threshold in connection with chronic contraction of muscle, in particular tooth clenching. Thus, according to this, the invention can be expressed as a method for treatment of tension-type headache in a person in need of such treatment, comprising interacting with neuronal transmission connected with pain perception so as to obtain a substantial increase of an otherwise unresponsive pain threshold in connection with chronic contraction of muscle, in particular tooth clenching.

Again, the interaction is preferably performed by administering a substance which will interact with neuronal transmission in a manner corresponding to what has been described above. The

substance can be characterized as a substance which performs positively (as described above), in the stimulus/response function test described above, or as a substance which, in a group of at least 20 patients suffering from tension type headache as defined above, will cause the effect of tooth clenching to be an increased pain threshold instead of an abnormally low pain threshold in at least 10 of the patients, preferably at least 12 of the patients, more preferably in at least 14 of the patients.

In another aspect, the invention relates to a substance having the properties defined herein for use as a medicament, in particular for the treatment of tension-type headache, This aspect relates to those substances or substance classes discussed herein which have not previously been used as medicaments or diagnostics. In a further aspect, the invention relates to the use of a substance having the properties described herein for the preparation of a pharmaceutical composition for the treatment or prophylaxis of tension-type headache.

The substance interacting with neuronal transmission to substantially normalize an otherwise qualitatively altered stimulus/response function in connection with nociception is preferably one which directly quantitatively lowers pain perception, in that, in a panel of test persons suffering from increased myofascial tenderness with disorder of pericranial muscle in connection with tension-type headache, the administration of the substance will result in transformation of a substantially linear pain intensity perception in response to pressure intensity in trapezius as well as other relevant pericranial muscles into a curve (C) of which the values of pain intensity are lower than the linear pain intensity perception.

The curve (C) is preferably a curve which can be described substantially as a power function and is a curve which is substantially linear in a double logarithmic plot.

It is preferred that substantially each of the values of curve (C) is at the most 20% higher, preferably at the most 10% higher, than the value of the corresponding curve produced for a test panel of healthy controls.

In connection with any of the patient panel tests discussed above it is noted that the treatment with the substance in question should be performed by administration at least once daily to maintain a therapeutic plasma level in the patients and should be continued for a sufficient time to allow the substance to exert its therapeutic effect, but that a substance is considered not to perform according to the particular test if the effect is not obtained within a treatment time of three months. This does not mean that it will necessarily take three months for a substance to exert its therapeutic effect; some compounds will show their therapeutic effect after much shorter treatment periods, down to days or even hours. In connection with testing of a new

candidate substance, the dosage of the substance will normally be kept as high as permitted by the toxicity of the compound during initial tests and will then be reduced to a lower level which is still maximally effective during the test proper.

Evaluation of the ability of a substance to provide an effective treatment for tension-type headache, by interacting with neuronal transmission according to the present invention, may also be performed as an acute test, in which the substance is administered, typically as a bolus or an infusion, to a group of patients suffering from chronic tension-type headache. In such a test, the pain connected to tension-type headache in these patients will typically be scored by the patients, as described in example 4, at various time points after administration of the substance, typically at least every 15 min and subsequently monitored over a period of at least 30 min, typically at least 60 min, preferrably at least 90, more preferably at least 120 min. For the evaluation of a candidate substance, an additional group of patients acutely suffering from tension-type headache will receive placebo and serve as a control group. The curves based on the pain scores of patients in both groups will typically be compared, as shown in Fig. 15, and a substance will be considered effective in treatment of tension-type headache according to the present invention, if it is capable of preventing or substantially preventing pain in connection with tension-type headache when pain scores after administration of the substance, when differering most from the corresponding score after administration of placebo, are at least 10% lower than scores for placebo, typically at least 20% lower, preferably at least 30% lower, more preferably at least 40% lower. For an evaluation as described here, the size of the participating groups of patients will be at least 5 patients in each group, typically at least 7 patients in each group, preferably at least 10 patients in each group, more preferably at least 12 patients in each group, even more preferably at least 15 patients in each group.

Evaluation of the ability of a substance to provide an effective profylaxis of tension-type headache by interacting with neuronal transmission according to the present invention can be performed as described above except that the parameter measured and scored by headache patients will typically be duration of pain or frequency of pain in connection with tension-type headache in sufferers with an episodic form of the disease.

In the practical treatment of a patient, the administration will normally be continued for at least one month, preferably at least two months and more preferably at least three months and in many cases indefinitely in order to establish and maintain the normalization which is aimed at. If the desired normalization occurs before one month of treatment, it is certainly possible according to the invention to discontinue the treatment, but this will increase risk of relapse and is normally not preferred. The administration is performed using at least one daily dosis or at any rate substantially at least one daily dosis (which means that the treatment is not outside the

scope of the invention if it is just interrupted one or perhaps even (but not preferred) a few days), and the dosis of the particular substance is preferably adapted so that it will maintain a therapeutic plasma level substantially at any time.

The interaction with neuronal transmission connected with pain perception will normally be such an interaction with neuronal transmission connected with second order nociceptive neurons which involves substantially reducing excitation mediated through the interaction between transmitter substances and their receptors on second order nociceptive neurons.

The above-mentioned interaction will normally involve a reduction of C-fiber, A-δ-fiber and A-β-fiber input to the nociceptive second order neurons, through a substantial reduction of excitatory activity in synapses of C-fibers, A-δ-fibers and A-β-fibers on second order neurons, said activity mediated through the interaction between the involved transmitter substances and their receptors on second order nociceptive neurons.

The reduction of excitatory activity in synapses of C-fibers, A-δ-fibers and A-β-fibers on second order neurons mediated through the interaction between the involved excitatory transmitter substances and their receptors on second order nociceptive neurons will preferably be performed by administration of an effective amount of at least one substance which a) substantially blocks the production of said excitatory transmitter substance, b) substantially blocks the release of said excitatory transmitter substance, c) substantially counteracts the action of said excitatory transmitter substance, and/or d) substantially blocks the relevant receptor for said excitatory transmitter substance.

Important examples of such excitatory transmitter substances are selected from the group consisting of glutamate, nitric oxide, neurokinins (substance P, neurokinin A, neurokinin B and bradykinin), CGRP, adenosine working through A2 receptors, 5-HT when working through 5-$HT_{2,3}$ receptors and pituitary adenylate cyclase actvating polypeptide (PACAP).

Substances which can interact with neurotransmission mediated by glutamate can be competitive or non-competitive antagonists of ionotropic glutamate receptors, including NMDA, AMPA and kainate receptors. Interaction with glutamate neurotransmission can also be performed with antagonists at the glycine site of the NMDA receptors or with antagonists or inverse agonists at modulatory sites such as polyamine sites. Interaction with metabotropic glutamate receptors can be performed with agonists or antagonists depending on whether they are receptors located pre or postsynaptically and whether they belong to the excitatory type I receptors (mGluR1,5) or the inhibitory type II and type III receptors (mGluR2,3 and mGluR4,6-8, respectively).

While sensitization of second order neurons is believed, as explained above, to be an important cause of pain in connection with tension type headache, it is clear that other elements of neural transmission may also play a significant role and in some cases even a predominant role as explained in the model described in connection with Fig. 1. Based on this recognition, another, more general, aspect of the present invention introduces, for the first time, the use of a number of classes of substances for treatment of tension type headache. This aspect relates to a method for treatment or prophylaxis of tension-type headache in a person in need of such treatment, comprising administering an effective amount of a substance which is a substance capable of decreasing or substantially preventing pain in connection with tension-type headache, and which, in the peripheral and/or central nervous system, is capable of specifically interacting with neuronal transmission connected with pain perception and which, in the peripheral and/or central nervous system, is further capable of

substantially blocking the production of glutamate or
substantially blocking the release of glutamate or
substantially counteracting the action of glutamate or
substantially blocking receptors for glutamate or
substantially blocking the production of 5-HT or
substantially blocking the release of 5-HT or
substantially counteracting the action of 5-HT or
substantially blocking 5-$HT_{2,3}$ receptors or
substantially enhancing the production of GABA or
substantially enhancing the release of GABA or
substantially enhancing the action of GABA or
substantially activating receptors for GABA or
substantially blocking the production of substance P or
substantially blocking the release of substance P or
substantially counteracting the action of substance P or
substantially blocking the receptors for substance P or
substantially blocking the production of nitric oxide or
substantially counteracting the action of nitric oxide or
substantially blocking the production of nitric oxide synthase (NOS) or
substantially counteracting the action of nitric oxide synthase (NOS) or
substantially blocking the production of guanylate cyclase or
substantially counteracting the action of guanylate cyclase or
substantially blocking the production of cyclic guanylate monophosphate (cGMP) or
substantially counteracting the action of cyclic guanylate monophosphate (cGMP) or
substantially blocking any further steps in the reaction induced by cyclic guanylate monophosphate (cGMP) or

substantially blocking the production of CGRP or
substantially blocking the release of CGRP or
substantially counteracting the action of CGRP or
substantially blocking receptors for CGRP or
substantially blocking the production of neurokinin A or
substantially blocking the release of neurokinin A or
substantially blocking the production of neurokinin B or
substantially blocking the release of neurokinin B or
substantially blocking the production of bradykinin or
substantially blocking the release of bradykinin or
substantially counteracting the action of bradykinin or
substantially blocking the receptors for bradykinin or
substantially blocking the production of PACAP or
substantially blocking the release of PACAP or
substantially counteracting the action of PACAP or
substantially blocking receptors for PACAP or
substantially blocking the production of adenosine or
substantially blocking the release of adenosine or
substantially counteracting the action of adenosine or
substantially blocking adenosine A2 receptors or
substantially enhancing the production of adenosine or
substantially enhancing the release of adenosine or
substantially enhancing the action of adenosine or
substantially activating adenosine A1 receptors or
substantially enhancing the production of galanine or
substantially enhancing the release of galanine or
substantially enhancing the action of galanine or
substantially activating receptors for galanine or
substantially enhancing the production of norepinephrine or
substantially enhancing the release of norepinephrine or
substantially enhancing the action of norepinephrine or
substantially activating receptors for norepinephrine or
substantially blocking the production of glycine or
substantially blocking the release of glycine or
substantially counteracting the action of glycine or
substantially blocking receptors for glycine or
substantially blocking the production of histamin or
substantially blocking the release of histamin or

substantially counteracting the action of histamin or
substantially blocking the receptors for histamin or
substantially blocking the production of neurotrophins or
substantially blocking the release of neurotrophins or
substantially counteracting the action of neurotrophins or
substantially blocking receptors for neurotrophins or
substantially blocking $Na^+$ ion channels or
substantially blocking $Ca^{2+}$ ion channels,

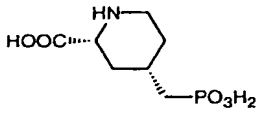
with the proviso that said substance is not Flupirtine.

An additional aspect of the present invention relates to a method of treatment of tension-type headache comprising administering to a person in need of such treatment an effective amount of a substance which substantially inhibits the action of the enzyme nitric oxide synthase (NOS) and thereby reduces chronic pain in connection with tension-type headache. In many cases the effect of treatment of tension-type headache with a NOS inhibitor will be exerted through a decrease in existing central sensitization, but also within the scope of the invention is treatment of tension-type headache with NOS inhibitors whose effect on the reduction of pain in connection with tension-type headache is mediated through a mechanism not directly involving inhibition of central sensitization. Such an alternative mechanism might possibly comprise an alteration of pain modulation involving nitric oxide.

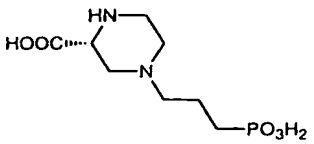
In the following discussion of substances or groups of substances and in the claims, numbers in parenthesis refer to the correspondingly numbered structural formulas in the formula sheets below.

## NMDA receptor antagonists

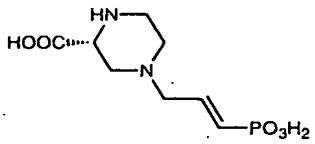
**competitive**



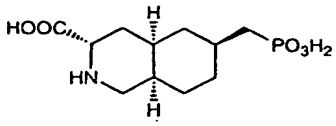
CGS 19755 (**1**)



(*R*)-CPP (**2**)

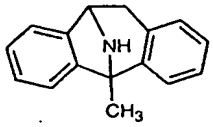


(*R*)-CPPene (**3**)

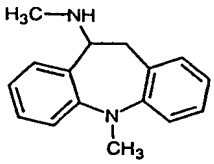


LY 235959 (**3a**)

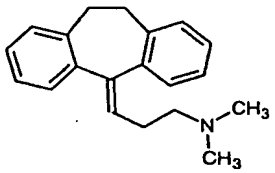
**non-competitive**



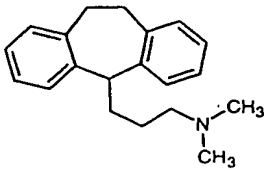
MK-801 (**4**)



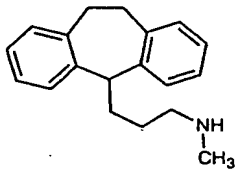
Metapramine (**4a**)



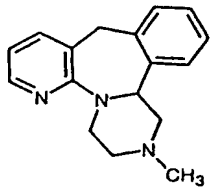
Amitriptyline (**4b**)



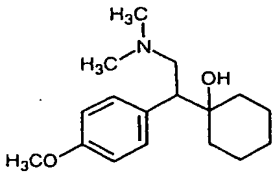
Imipramine (**4c**)



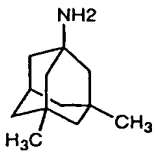
Desipramine (**4d**)



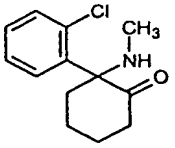
Mirtazapine (**4e**)



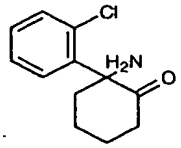
Venlafaxine (**4f**)



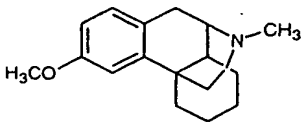
Memantine (**5**)



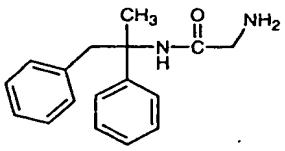
Ketamine (**6**)



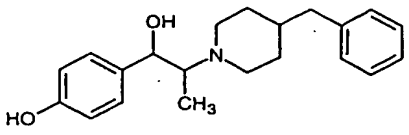
Norketamine (**7**)



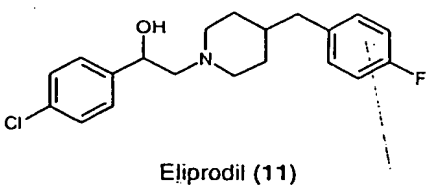
Dextromethorphan (**8**)



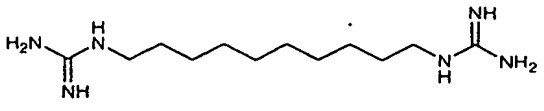
Remacemide (**9**)



Ifenprodil (**10**)

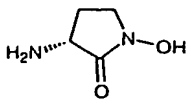


Eliprodil (**11**)

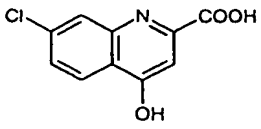


Synthalin (**11a**)

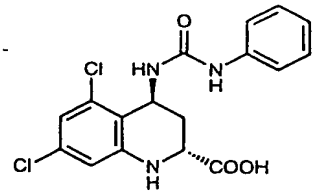
**Glycine antagonists (NMDA co-agonist site)**



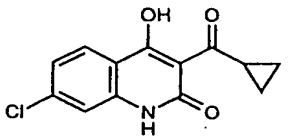
(*R*)-HA-966 (**12**)



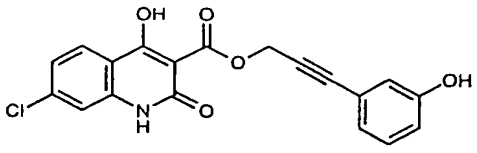
7-Cl-Kynurenic acid (**13**)



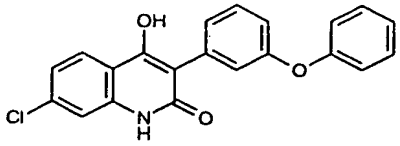
L-689,560 (**14**)



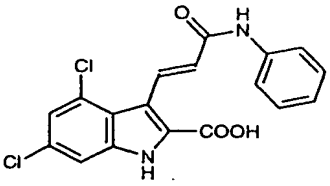
L-701,252 (**14a**)



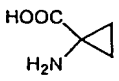
L-701,273 (**14b**)



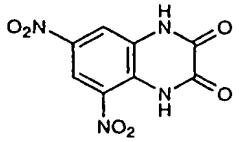
L-701,324 (**14c**)



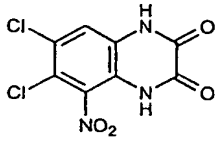
GV150526A (**14d**)



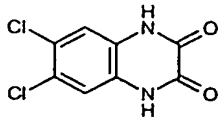
ACPC (**15**)



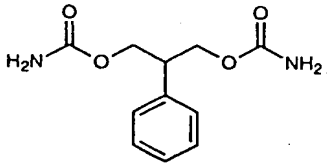
MNQX (**16**)



ACEA1021 (**17**)



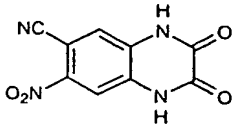
DCQX (**17a**)



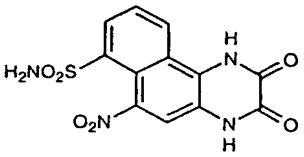
Felbamate (**18**)

**AMPA receptor antagonists**

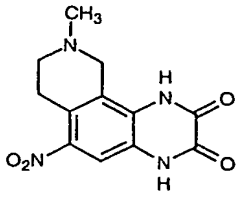
**competitive**



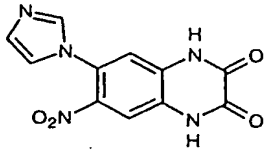
CNQX (**19**)



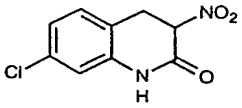
NBQX (**20**)



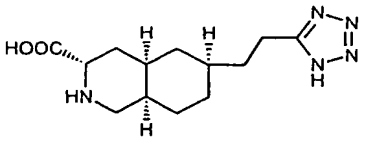
PNQX (**21**)



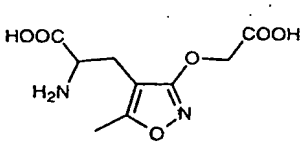
YM90K (**22**)



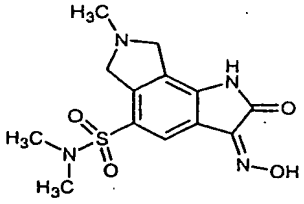
L-698,544 (**23**)



LY 215490 (**24**)

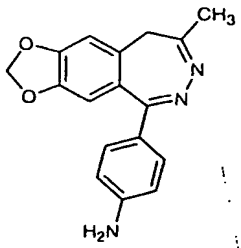


AMOA (**25**)

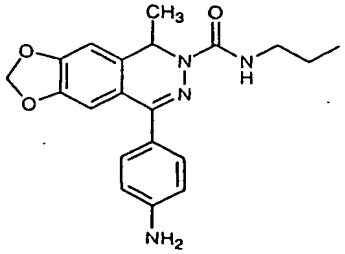


NS-257 (**26**)

**non-competitive**

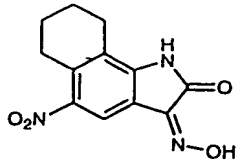


GYKI 52466 (**27**)



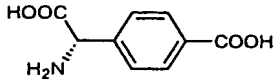
SYM 2206 (**28**)

**Kainic acid receptor antagonist**

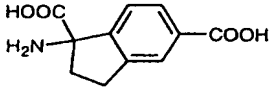


NS-102 (**29**)

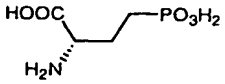
**Metabotropic glutamate receptor ligands**



4CPG (**30**)



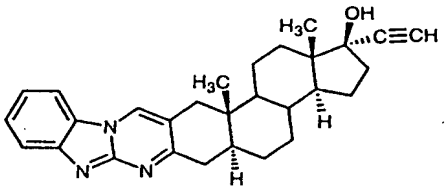
UPF523 (**31**)



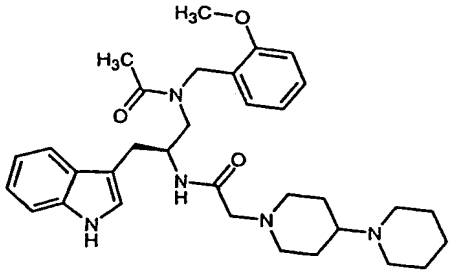
L-AP4 (**32**)

**Substance P ($NK_1$) and Neurokinin A ($NK_2$) receptor antagonists**

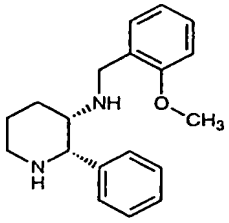
**$NK_1$ receptor antagonists**



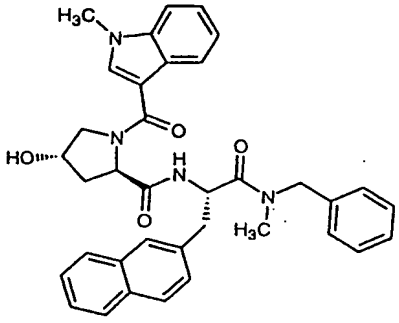
WIN 51,708 (**33**)



LY 303870 (**34**)

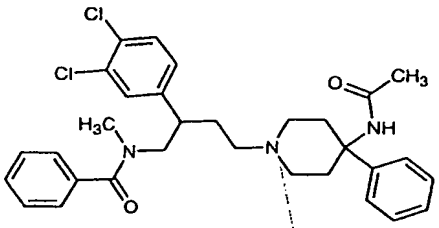


CP 99,994 (**35**)

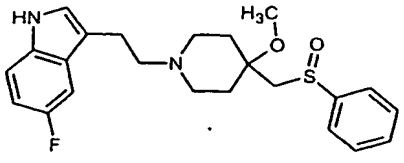


FK 888 (**36**)

**$NK_2$ receptor antagonists**



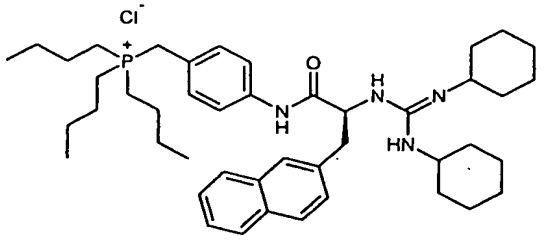
SR-48968 (**37**)



GR 159897 (**38**)

## Bradykinin receptor antagonists

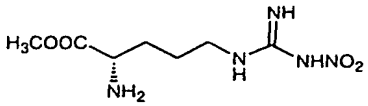
D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic



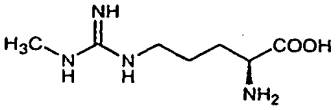
Icatibant (**39**)

WIN 64338 (**40**)

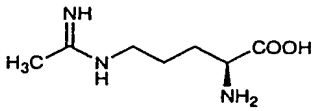
## NO synthase inhibitors



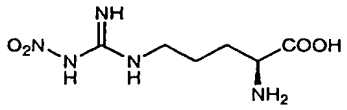
L-NAME (**41**)



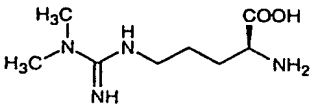
L-NMMA (**41a**)



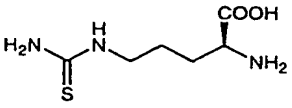
L-NIO (**41b**)



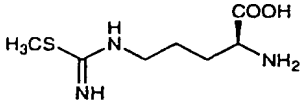
L-NNA (**41c**)



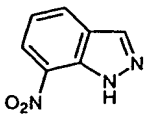
Dimethyl-L-arginine (**41d**)



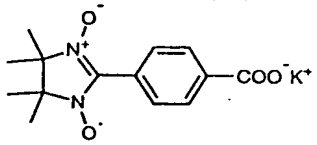
Thiocitrulline (**42**)



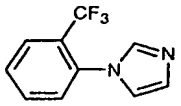
(*S*)-Methylthiocitrulline (**42a**)



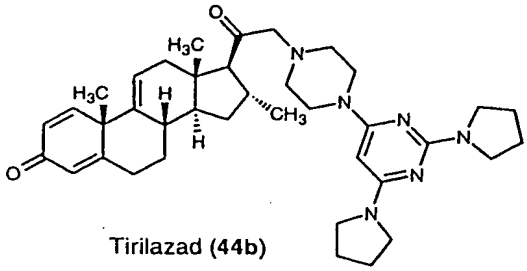
7-Nitroindazole (**43**)



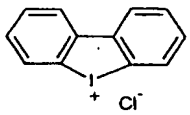
Potassium carboxy-PTIO (**44**)



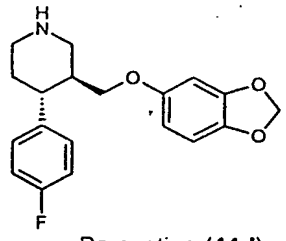
TRIM (**44a**)



Tirilazad (**44b**)

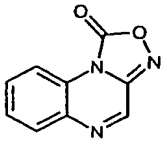


Diphenyleneiodonium chloride (**44c**)



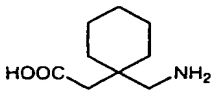
Paroxetine (**44d**)

## Guanylat cyclase inbibitor

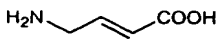


ODQ (**45**)

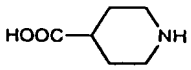
## GABA-A receptor agonists



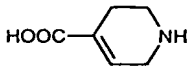

Gabapentin (**46**)



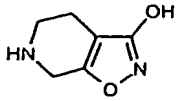

TACA (**46a**)



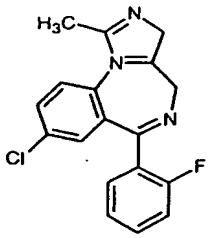

Isonipecotic acid (**47**)




Isoguvacine (**48**)

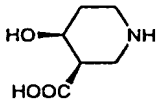



THIP (**49**)

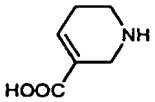



Midazolam (**49a**)

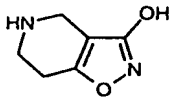
## GABA uptake inhibitors



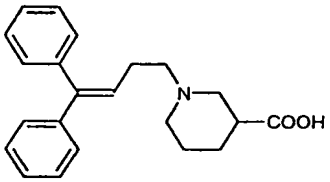

(±)-cis-4-Hydroxynipecotic acid (**50**)



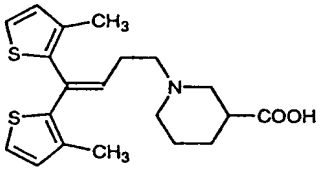

Guvacine (**51**)



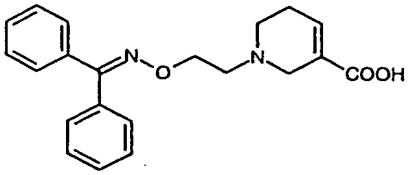

THPO (**52**)




SKF 89976-A (**53**)

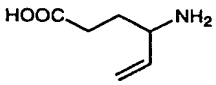



Tiagabine (**54**)



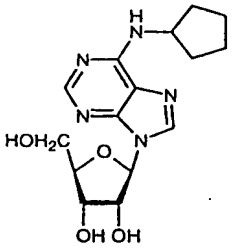

NO-711 (**54a**)

## GABA transaminase inhibitor

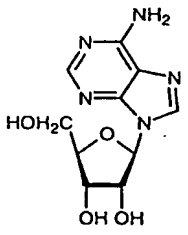



Vigabatrin (**55**)

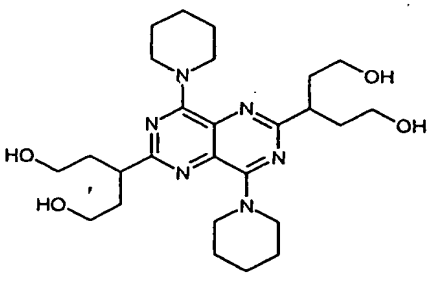
## Adenosin receptor ligands



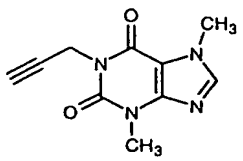

$N^6$-Cyclopentyladenosine (**56**)



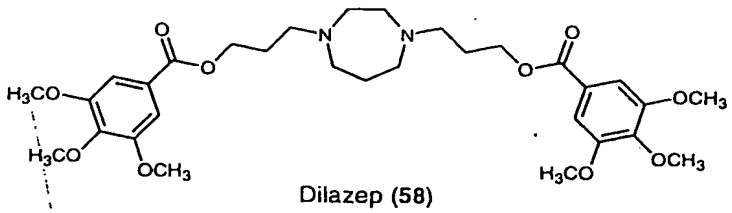

Adenosine (**56a**)




Dipyridamole (**56b**)

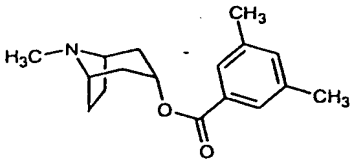



DMPX (**57**)

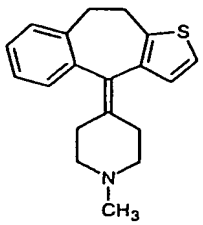



Dilazep (**58**)

**5-$HT_{2,3}$ receptor antagonists**

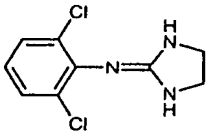


Tropanserin (**59**)

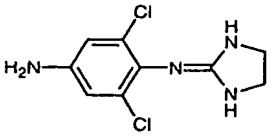


Pizotyline (**60**)

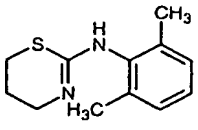
**α-2 Receptor agonists**



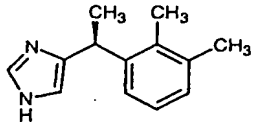
Clonidine (**61**)



Apraclonidine (**62**)

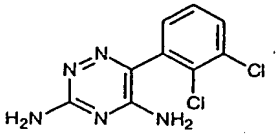


Xylazine (**63**)

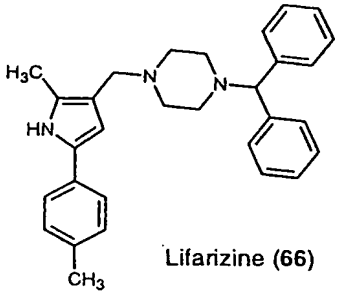


Dexmedetomidine (**64**)

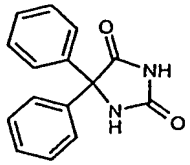
**$Na^{+}$ channel blockers**



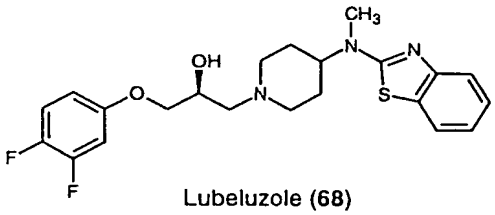
Lamotrigine (**65**)



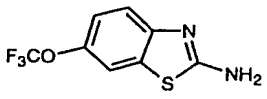
Lifarizine (**66**)



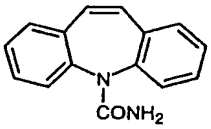
Phenytoin (**67**)



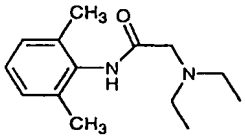
Lubeluzole (**68**)



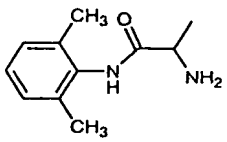
Riluzole (**69**)



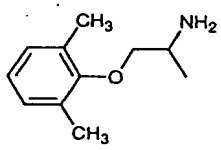
Carbamazepine (**70**)



Lidocaine (**71**)

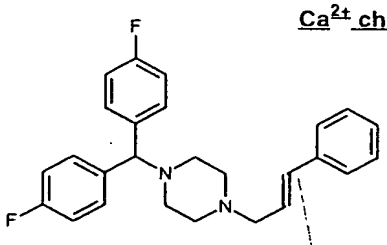


Tocainide (**72**)

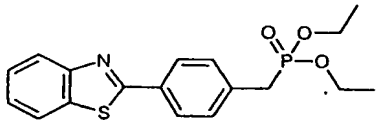


Mexiletene (**73**)

**$Ca^{2+}$ channel blockers**



Flunarizine (**74**)



Fostedil (**75**)

Examples of competitive NMDA receptor antagonists are CGS 19755 (1), (*R*)-CPP (2), (*R*)-CPPene (3), LY 235959 (3a)

Examples of non-competitive NMDA receptor antagonists are MK-801 (4), Metapramine (4a), Amitryptyline (4b), Imipramine (4c), Desipramine (4d), Mirtazapine (4f), Venlafaxine (4e), Memantine (5), Ketamine (6), Norketamine (7), Dextromethorphane (8), Remacemide (9), Ifenprodil (10), Eliprodil (11), Synthalin (11a), Pizotyline (60), and Gabapentine (46).

Mirtazapine (4c) and Venlafaxine (4d) are conventionally known to have α-2 receptor antagonist effects, and their efficacy as antidepressants are thought to be exerted through a decrease in noradrenergic neurotransmission. However, it is presently believed that Mirtazapine and Venlafaxine may also have an effect on glutamate neurotransmission, potentially as non-competitive NMDA receptor antagonists. It is through this mechanism that the two substances are presumed to provide a method of treatment of tension-type headache according to the present invention.

Examples of Glycine antagonists are (R)-HA-966 (12), 7-Cl-Kynurenic acid (13), L-689,560 (14), L-701,252 (14a), L-701,273 (14b), L-701,324 (14c), GV150526A (14d), ACPC (15), MNQX (16), ACEA 1021 (17), DCQX (17a), Felbamate (18).

Examples of competitive AMPA receptor antagonists are CNQX (19), NBQX (20), PNQX (21), YM90K (22), L-698,544 (23), LY 215490 (24), AMOA (25), NS-257 (26)

Examples of non-competitive AMPA receptor antagonists are GYKI 52466 (27), SYM 2206 (28)

An example of a competitive kainate receptor antagonist is NS-102 (29)

Examples of metabotropic receptor agonists are 4CPG (30), UPF523 (31), L-AP4 (32)

Substances which can interact with excitatory neurotransmission mediated by 5-HT can a) substantially block the synthesis of 5-HT, b) substantially block the release of 5-HT, c) substantially counteract the action of 5-HT and/or d) substantially function as antagonists at excitatory 5-HT 5-$HT_{2,3}$ receptors.

Examples of 5-$HT_{2,3}$ receptor antagonists are Tropanserin (59), Pizotyline (60).

It is presently believed that Pizotyline (60) may also have effect on glutamete transmission, potentially as a non-competitive NMDA receptor antagonist, as mentioned above. This

mechanism is presumed, in addition to the 5-HT receptor antagonism, to provide a method of treatment of tension-type headache according to the present invention.

Substances which can interact with excitatory neurotransmission mediated by adenosine can a) substantially block the synthesis of adenosine, b) substantially block the release of adenosine, c) substantially counteract the action of adenosine, and/or d) substantially function as antagonists at adenosine A2 receptors.

Examples of adenosine A2 receptor antagonists are DMPX **(57)** and Dilazep **(58)**.

Substances which can interact with neurotransmission mediated by substance P can a) substantially block the synthesis of substance P, b) substantially block the release of substance P, c) substantially counteract the action of substance P, and/or d) be competitive or non-competitive antagonists of substance P receptors ($NK_1$ receptors).

Examples of substance P ($NK_1$) receptor antagonists are WIN 51,708 **(33)**, LY 303870 **(34)**, CP 99,994 **(35)**, FK 888 **(36)**

Substances which can interact with neurotransmission mediated by neurokinin A can a) substantially block the synthesis of neurokinin A, b) substantially block the release of neurokinin A, c) substantially counteract the action of neurokinin A, and/or d) be competitive or non-competitive antagonists of neurokinin A receptors ($NK_2$ receptors).

Examples of neurokinin A ($NK_2$) receptor antagonists are SR-48968 **(37)**, GR 159897 **(38)**

Substances which can interact with neurotransmission mediated by bradykinin can a) substantially block the synthesis of bradykinin, b) substantially block the release of bradykinin, c) substantially counteract the action of bradykinin, and/or d) be competitive or non-competitive antagonists of bradykinin receptors.

Examples of bradykinin receptor antagonists are Icatibant **(39)**, WIN 64338 **(40)**

Substances which can interact with neurotransmission mediated by CGRP can a) substantially block the synthesis of CGRP, b) substantially block the release of CGRP, c) substantially counteract the action of CGRP, and/or d) be competitive or non-competitive antagonists of CGRP receptors.

Examples of GCRP receptor antagonists are GCRP 8-37.

Substances which can interact with neurotransmission mediated by PACAP can a) substantially block the synthesis of PACAP, b) substantially block the release of PACAP, c) substantially counteract the action of PACAP, and/or d) be competitive or non-competitive antagonists of PACAP receptors.

Substances which can interact with neurotransmission mediated by nitric oxide can a) substantially block the synthesis of nitric oxide, and/or b) substantially counteract the action of nitric oxide.

The interaction with neuronal transmission connected with pain perception connected with second order nociceptive neurons can comprise interaction with intracellular substances involved in this neuronal transmission, said interaction involving excitation mediated through the interaction with enzymes and second messengers in second order nociceptive neurons.

Preferred examples of the above mentioned intracellular substances are NOS, guanylate cyclase, and cGMP.

The interaction with neuronal transmission connected with pain perception, comprising interaction with NOS will preferably be performed by the administration of an effective amount of at least one substance which substantially a) blocks the production of the NOS, and/or b) substantially counteracts the action of NOS.

Examples of NOS inhibitors are L-NAME **(41)**, L-NMMA **(41a)**, L-NIO **(41b)**, L-NNA **(41c)**, Dimethyl-L-arginine **(41d)**, Thiocitrulline **(42)**, (*S*)-Methylthiocitrulline **(42a)**, 7-Nitroindazole **(43)**, Potassium carboxy-PTIO **(44)**, TRIM **(44a)**, Tirilazad **(44b)**, Diphenyleneiodinium chloride **(44c)**, Paroxetine **(44d)**.

The interaction with neuronal transmission connected with pain perception, comprising interaction with guanylate cyclase can be performed by the administration of an effective amount of at least one substance which substantially a) blocks the production of the guanylate cyclase, and/or b) substantially counteracts the action of guanylate cyclase.

Examples of guanylate cyclase inhibitors are ODQ **(45)**

The interaction with neuronal transmission connected with pain perception comprising interaction with cGMP can be executed by the administration of an effective amount of at least

one substance which substantially a) blocks the production of the cGMP, b) substantially counteracts the action of cGMP, and/or c) substantially blocks any further steps in the reaction induced by cGMP, such as protein kinase C.

The activity of C-fibers, A-δ-fibers and A-β-fibers on second order nociceptive neurons involves inhibitory neurotransmitter substances. Reduction of activity of C-fibers on second order neurons will normally be performed by administration of an effective amount of at least one substance which a) substantially inhibits the enzymatic degradation of said inhibitory transmitter substance, b) substantially enhances the release of said inhibitory transmitter substance, c) substantially enhances the action of said inhibitory transmitter substance and/or substantially activates the relevant receptor for said inhibitory transmitter substance.

Preferred examples of such inhibitory transmitter substances are selected from the group consisting of GABA, galanine, adenosine working through $A^1$ receptors, and norepinephrine.

Substances which can interact with neurotransmission mediated by GABA can a) substantially inhibit the enzymatic degradation of GABA, b) substantially enhance the release of GABA, c) substantially enhance the action of GABA and/or substantially function as agonists at GABA-A receptors.

An example of a substance with GABA-enhancing activity is Midazolam **(49a)**.

Examples of GABA-A receptor agonists are Gabapentin **(46)**, TACA **(46a)**, Isonipecotic acid **(47)**, Isoguvacine **(48)**, THIP **(49)**.

Gabapentin is conventionally known to have GABA-A receptor agonist activity, though this mechanism has been questioned. However, it is presently believed that Gabapentin may also have antagonist effect on glutamate transmission, indirectly or directly, potentially as a non-competitive NMDA receptor antagonist, as mentioned above. It is through this mechanism, in addition to its gabaérgic activity, that Gabapentin is presumed to provide a method of treatment of tension-type headache according to the present invention.

Examples of GABA uptake inhibitors are (+/-)-cis-4-Hydroxynipecotic acid **(50)**, Guvacine **(51)**, THPO **(52)**, SKF 89976-A **(53)**, Tiagabine **(54)**, NO-711 **(54a)**.

Examples of GABA transaminase inhibitors are Vigabatrin **(55)**

Substances which can interact with neurotransmission mediated by galanine can a) substantially inhibit the enzymatic degradation of galanine, b) substantially enhance the release of galanine, c) substantially enhance the action of galanine and/or substantially function as agonists at galanine receptors.

Substances which can interact with inhibitory neurotransmission mediated by adenosine can a) substantially inhibit the enzymatic degradation of adenosine, b) substantially enhance the release of adenosine, c) substantially enhance the action of adenosine and/or d) substantially function as agonists at $A^1$ receptors.

Examples adenosine $A^1$ receptor agonists are N6-Cyclopentyladenosine **(56)**, Adenosine **(56a)**.

An example of an enhancer of the action of adenosine is Dipyridamole **(56b)**.

Substances which can interact with neurotransmission mediated by norepinephrine can a) substantially inhibit the enzymatic degradation of norepinephrine, b) substantially enhance the release of norepinephrine, c) substantially enhance the action of norepinephrine and/or substantially function as agonists at norepinephrine $\alpha$-2 receptors.

Examples of $\alpha$-2 receptor agonists are Clonidine **(61)**, Apraclonidine **(62)**, Xylazine **(63)**, Dexmedetomidine **(64)**.

Reduction of activity of C-fibers on second order nociceptive neurons can be performed by administration of an effective amount of at least one substance which substantially blocks ion channels for $Na^+$ or $Ca^{2+}$ ions.

Examples of $Na^+$ channel blockers are Lamotrigine **(65)**, Lifaizine **(66)**, Phentytoin **(67)**, Lubeluzole **(68)**, Riluzole **(69)**, Carbamazepine **(70)**, Lidocaine **(71)**, Tocainide **(72)**, Mexiletene **(73)**

Examples of $Ca^{2+}$ channel blockers are Flunarizine **(74)**, Fostedil **(75)**.

In addition to the specific substances mentioned above, derivatives thereof which show an activity of the same kind as the substance specifically mentioned are also useful for the purpose of the present invention. The kind of derivatives which come into consideration will, of course, depend on the specific character of the substance in question, but as general examples of derivatives which may be relevant for many of the substances may be mentioned introduction of or change of alkylsubstituents (typically with a chain length from one to five carbon atoms) on

aliphatic chains, cycloalkanes, aromatic and heterocyclic ring systems, introduction of or change of substituents such as halogens or nitro groups, change of ringsize for cycloalkanes, change of aromatic or heterocyclic ringsystems, change of alkylsubstituents on O-and N-atoms, change of the alcohol part of ester groups, and bioisosteric replacement of functional groups, especially use of carboxylic acid bioisosteres such as phosphonic acids, phosphinic acids, tetrazoles, 3-hydroxyisoxazoles, sulphonamiders and hydroxyamic acids. Salts of acidic or basic compounds will be equally usefull compared to the free acids or free bases. In case of racemic compounds, can racemates as well as pure enantiomeres and diastereoisomeres be used, and in the case of substances interacting with antagonist action be required. Of course, derivatives to be used should be derivatives which, in addition to their desired activity, show an acceptably low toxicity, and, in general, the derivates should, just as the substances themselves, be pharmaceutically acceptable.

The substance used according to the invention may be administered as such or in the form of a suitable prodrug thereof. The term "prodrug" denotes a bioreversible derivative of the drug, the bioreversible derivative being therapeutically substantially inactive per se but being able to convert in the body to the active substance by an enzymatic or non-enzymatic process.

Thus, examples of suitable prodrugs of the substances used according to the invention include compounds obtained by suitable bioreversible derivatization of one or more reactive or derivatizable groups of the parent substance to result in a bioreversible derivative. The derivatization may be performed to obtain a higher bioavailability of the active substance, to stabilize an otherwise unstable active substance, to increase the lipophilicity of the substance administered, etc.

Examples of types of substances which may advantageously be administered in the form of prodrugs are carboxylic acids, other acidic groups and amines, which may be rendered more lipophilic by suitable bioreversible derivatization. As examples of suitable groups may be mentioned bioreversible esters or bioreversible amides. Amino acids are typical examples of substances which, in their unmodified form, may have a low absorption upon administration. Suitable prodrug derivatives of amino acids will be one or both of the above-mentioned types of bioreversible derivatives.

For the administration to a patient, a substance having any of the activities as defined above or a prodrug thereof is preferably formulated in a pharmaceutical composition containing one or more substances having any of the activities as defined above or prodrugs thereof and one or more pharmaceutically acceptable excipients.

The substance or substances to be administered may be formulated in the compositions in pharmaceutically acceptable media, the character of which are adapted to the chemical character of the substance. The compositions may be adapted for administration by any suitable method, for example by oral, buccal, sublingual, nasal, rectal or transdermal administration. Substances which are suitable for oral administration may be formulated as liquids or solids, such as syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid compositions will normally comprise a suspension or solution of the substance in a suitable liquid carrier or suitable liquid carriers, for example an aqueous solvent such as water, ethanol or glycerol, or a non-aqueous solvent, such as polyethylene glycol or an oil. The composition may also contain a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be made using any suitable pharmaceutical carrier or carriers used for preparing solid formulations, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable non-toxic composition may be formed by incorporating normally used excipients, such as those carriers previously listed, and generally 1-95% of active ingredient, that is, a substance used according to the invention or a prodrug thereof, often preferably 25-75% of the substance of the prodrug. A composition in the form of a capsule can be prepared using conventional encapsulation procedures. Thus, e.g., pellets containing the substance or prodrug in question may be prepared using any suitable carriers and then filled into a hard gelatin capsule, or a dispersion or suspension can be prepared using any suitable pharmaceutical carrier or carriers, such as aqueous gums, celluloses, silicates or oils and the dispersion or suspension can be filled into a soft gelatin capsule.

Examples of parenteral compositions are solutions or suspensions of the substances or prodrugs in a sterile aqueous carrier or parenterally acceptable oil, such as polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as buffering agents, wetting agents, detergents, and the like. Additives may also include additional active ingredients, e.g. bactericidal agents, or stabilizers. If desired, the solution or suspension can be lyophilized and reconstituted with a suitable carrier such as a sterile aqueous carrier prior to administration.

Compositions for nasal administration can be formulated, e.g., as aerosols, drops, gels and powders. For aerosol administration, the substance or prodrug is preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of the substance or prodrug are 0.01-20% by weight, preferably 1-10%. The surfactant must, of course, be non-toxic, and preferably soluble in the propellant. Representative of such surfactants are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic,

lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride such as, for example, ethylene glycol, glycerol, erythritol, arbitol, mannitol, sorbitol, the hexitol anhydrides derived from sorbitol, and the polyoxyethylene and polyoxypropylene derivatives of these esters. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute 0.1-20% by weight of the composition, preferably 0.25-5%. The balance of the composition is ordinarily propellant. Liquified propellants are typically gases at ambient conditions, and are condensed under pressure. Among suitable liquified propellants are the lower alkanes containing up to 5 carbons, such as butane and propane; and preferably fluorinated or fluorochlorinated alkanes. Mixtures of the above may also be employed. In producing the aerosol, a container equipped with a suitable valve is filled with the appropriate propellant, containing the substance according to the invention and surfactant. The ingredients are thus maintained at an elevated pressure until released by action of the valve.

Compositions for buccal or sublingual administration are, for example, tablets, lozenges and pastilles, in which the substance or the prodrug is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerol. Compositions for rectal administration are suitably in the form of suppositories containing a suppository base such as cocoa butter. Compositions for transdermal application are for example ointments, gels and transdermal patches.

The compositions are preferably in unit dosage form such as a tablet, capsule or ampoule. Each dosage unit for oral administration will normally contain from 1 to 500 mg (and for parenteral administration preferably from 0.1 to 25 mg) of a substance used according to the invention or a prodrug therefor, calculated as the free active substance.

The physiologically acceptable substances or prodrugs are normally administered in a daily dosage of between 1 mg and 500 mg for a grown-up person, usually between 10 mg and 400 mg, such as between 10 mg and 250 mg orally, or an intravenous, subcutaneous or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 and 50 mg, such as between 1 mg and 25 mg of the substance. The substance or prodrug is preferably administered 1 to 4 times daily. As mentioned above, the administration is normally aimed at maintaining a therapeutically effective serum concentration of the substance for at least one month, preferably at least two months or at least three months. Controlled release type compositions will often be suitable for maintaining an effective serum concentration with a small number of daily unit dosages.

## LEGENDS TO FIGURES

Figure 1 shows the model for the development of tension-type headache.
Abbreviations; V: Trigeminal nerve, C2 and C3: Second and third cervical segment of the spinal cord, PAG: Periaquaductal grey, DRN: Dorsal raphe nuclei, on-cells: cells in ventromedial medulla, which activate pain pathways, for instance by reducing the threshold in the tail flick test. C: C fibers. Aδ: A-δ-fibers. Aβ: A-β-fibers.

Figure 2 shows a palpometer with Force Sensing Resistor.
A) The palpometer consists of a Force Sensing Resistor connected to a meter. The force is recorded by the meter scale, which is divided into arbitrary units from 60 U to 200 U;

B) The Force Sensing Resistor is a thin polymer film device, which is attached to the fingertip by means of thin adhesive tape (Micropore®, not shown).

Figure 3 depicts stimulus-response functions in trapezius muscle.
Stimulus-response functions for pressure versus pain in the trapezius muscle in 40 patients with chronic tension-type headache (dots) and in 40 control subjects (triangles)(mean ± SE). Patients were significantly more tender than controls, $P=0.002$. In patients, the stimulus-response function was approximately linear with a slope ($\beta$) $=0.50\pm0.04$ mm/U, $P=0.00004$. In contrast, pain intensities increased in a positively accelerating fashion with increasing pressure intensities in controls, a relation that was well described by a power function. This was demonstrated by obtaining an approximately linear relation between pressure and pain in a double logarithmic plot, $\beta=3.8\pm0.61$ logmm/logU, $P=0.002$ (inset).

Figure 4 depicts stimulus-response functions in temporal muscle.
Stimulus-response functions for pressure versus pain in the temporal muscle in 40 patients (dots) and in 40 controls (triangles)(mean ± SE). Patients were slightly more tender than controls, but the difference was not statistically significant, $P=0.42$. In both groups, pain intensities increased in a positively accelerating fashion with increasing pressure intensities. This was demonstrated by obtaining approximately linear relations between pressure and pain in a double logarithmic plot: patients $\beta=3.0\pm0.36$ logmm/logU, $P=0.0002$; controls $\beta=6.7\pm0.36$ logmm/logU, $P=0.00001$ (inset).

Figure 5 depicts stimulus-response functions in trapezius muscle.
Stimulus-response functions for pressure versus pain in the trapezius muscle in the 20 most tender patients (diamonds) and in the 20 least tender patients (squares)(mean ± SE). In the most tender patients, the stimulus-response function was linear, $\beta=0.69\pm0.03$ mm/U,

$P < 0.00001$. In contrast, pain intensities increased in a positively accelerating fashion with increasing pressure intensities in the least tender patients. This was demonstrated by obtaining a linear relation between pressure and pain in a double logarithmic plot, $\beta = 4.0 \pm 0.18$ logmm/logU, $P < 0.00001$ (inset).

Figure 6 shows Total Tenderness Scores in patients.
The Total Tenderness Scores(TTS) in patients outside and during a headache episode and in controls. Median values are given (*** indicate $p < 10^{-5}$ and ** indicate $p = 0.01$, Wilcoxon´s test).

Figure 7 shows Pressure Pain Thresholds (PPDT) and Pressure Pain Tolerances (PPTO) in patients.
Pressure Pain Thresholds (PPDT) and Pressure Pain Tolerances (PPTO) in patients outside(closed bars) and during a headache episode(open bars). Mean values of left and right side are given in kPa with SD as vertical bars(* indicate $p < 0.05$, Wilcoxon´s test).

Figure 8 shows thermal thresholds in the hands and temporal (Temp) regions of patients.
Thermal thresholds in the hands and temporal (Temp) regions of patients outside(closed bars) and during a headache episode(open bars). WD indicate warmth detection, HPD heat pain detection and HPTO heat pain tolerance thresholds. Mean values of left and right side are given in $^{o}C$ with SD as vertical bars
(* indicate $p < 0.05$, Wilcoxon´s test).

Figure 9 depicts EMG-amplitude levels from the temporal and trapezius muscles of patients.
EMG-amplitude levels from the temporal and trapezius muscles of patients outside (closed bars) and during a headache episode (open bars). Part A indicates the resting condition and part B the maximal voluntary contraction. Mean values of left and right side are given in uV with SD as vertical bars.

Figure 10 depicts pain intensities in patients and controls.
Pain intensities in those patients(filled circles) and controls(open circles) who developed tension-type headache after a 30 minutes sustained clenching procedure. The ordinate indicates the mean pain intensity in mm as recorded on a 100 mm visual analogue scale. The abscissa indicates the time after the clenching procedure(* $p < 0.05$, Mann-Whitney´s test)

Figure 11 shows Total Tenderness Scores(TTS) in patients and in controls.

Total Tenderness Scores(TTS) in patients and in controls before and 90 minutes after experimental tooth clenching with respect to development of headache. Median values with quartiles are given. (** indicate $p<0.01$, *** $p<0.001$, Wilcoxon´s test).

Figure 12 shows Pressure Pain Detection Thresholds and Pressure Pain Tolerances in patients and controls.
Part A shows the Pressure Pain Detection Thresholds and Part B the Pressure Pain Tolerances from fingers(F), temporal(T) and parietal(P) regions from patients and controls before (filled bars) and after clenching (open bars) with respect to development of headache. Mean values of right and left side with SD are given in kPa. (* indicate $p<0.05$, ** $p<0.01$, Wilcoxon´s test).

Figure 13 shows thermal thresholds in the temporal region of patients and controls.
Thermal thresholds in the temporal region of patients and controls before(filled bars) and after clenching(open bars) with respect to headache development. WD indicate warmth detection, PD heat pain detection and PTO heat pain tolerance. Mean values of right and left side with SD are given in °C.

Figure 14 shows EMG-amplitudes in temporal and trapezius muscles of patients and controls.
Part A shows the EMG-amplitudes (Root Mean Square-values) during resting condition and part B during the maximal voluntary contraction in temporal(temp) and trapezius(trap) muscles from patients and controls before (filled bars) and after clenching(open bars) with respect to headache development. Mean values of left and right side with SD are given in uV (* indicate $p<0.05$, ** $p<0.01$ and *** $p<0.001$, Wilcoxon´s test).

Figure 15 shows changes in pain intensity after treatment.
Post infusion changes in pain intensity (VAS) relative to pre-treatment pain intensity in 16 patients with chronic pain. L-NMMA reduced pain significantly more than placebo ($p=0.007$).

Figure 16 shows Pressure Pain Thresholds (PPDT) and Pressure Pain Tolerances (PPTO) in patients with chronic tension-type headache associated with muscular disorders (MUS) (filled bars) or unassociated with such disorders (non-MUS) (open bars). Mean values from the fingers, temporal (Temp) and Parietal (Par) regions are given in kPa with SE as vertical bars (*** indicate $p<0.001$,* indicate $p=0.04$).

Figure 17 shows Pressure Pain Thresholds (PPDT) and Pressure Pain Tolerances (PPTO) in patients with episodic tension-type headache associated with muscular disorders(MUS)(filled bars) or unassociated with such disorders(non-MUS)(open bars). Mean values from fingers, temporal(Temp) and Parietal(Par) regions are given in kPa with SE as vertical bars.

No significant differences were detected.

## EXAMPLE 1

## EXPERIMENTAL EVIDENCE FOR CENTRAL SENSITIZATION IN CHRONIC MYOFASCIAL PAIN

The study was performed in order to investigate the pathophysiology of myofascial tenderness, which has consistently been reported to be increased in patients with tension-type headache (Lous and Olesen 1982; Langemark and Olesen 1987; Jensen et al. 1993b). Recently, it was suggested that myofascial tenderness may be the result of a lowered pressure pain threshold, a stronger response to pressures in the noxious range (as illustrated by a steeper stimulus-response function) or a combination of both (Jensen 1990b). The aim of the study therefore was to investigate the stimulus-response function for pressure versus pain in patients with tension-type headache. The methods and the results of the study will be described in the following.

### MATERIALS AND METHODS

**Table III.** Clinical data on headache patients and controls

| | Patients | Controls |
|---|---|---|
| Number | 40 | 40 |
| Sex (females/males) | 25/15 | 25/15 |
| Age, years | 40.0 (18-60) | 39.8(18-60) |
| Frequency of TH, days/4 weeks | 24.6 (16-28) | < 1 |

*Patients and controls*

Forty patients with chronic tension-type headache diagnosed according to the criteria of the International Headache Society (1988) were examined during a typical episode of tension-type headache (Table III). Seven patients with coexisting infrequent migraine (≤ one day/month) were accepted. The patients were recruited from the out-patient headache clinic at Glostrup Hospital without respect to presence or absence of myofascial tenderness. All patients underwent a general physical and a neurological examination and completed a diagnostic headache diary (Russell et al. 1992) during a 4-week run-in period. The patients were not allowed to take analgesics on the day of examination. Patients suffering from serious somatic or psychiatric diseases and abusers of analgesics were excluded. Forty healthy, age- and sex-

matched volunteers served as controls. Only controls who did not have a headache on the day of examination and had less than 12 days with headache a year were used. All subjects gave written informed consent to participate in the study, which was approved by the local ethics committee.

*Apparatus*

A palpometer (Fig. 2)(Bendtsen et al. 1994) was used to investigate the stimulus-response function for pressure versus pain. The palpometer consists of a Force Sensing Resistor ™ (FSR) connected to a meter, a principle first described by Atkins et al. (Atkins et al. 1992). The FSR is a commercially available polymer film device, which exhibits a decreasing electrical resistance with increasing force applied to the device. If the force is concentrated on a small area the resistance is further decreased, i.e. the properties of the FSR lies somewhere between a force transducer and a pressure transducer. The FSR is 0.33 mm thick and circular with a diameter of 10 mm. The FSR is attached with thin adhesive tape (Micropore®) to the tip of the palpating finger. The force applied to the FSR is displayed on the meter scale, which is divided into arbitrary units from 60 to 200 arbitrary units (U). To improve the readability of the meter, the readout is filtered using a low-pass filter. The relation between the forces applied to the plastic film and the palpometer output is linear in the range from 80 to 200U (Bendtsen et al. 1994). This range is equivalent to a force range from 235 gm to 1550 gm. The intra- and inter-observer variations for recordings of pressure intensity have previously found to be 3.1% and 7.2%, respectively (Bendtsen et al. 1994). Detailed information on the palpometer has been published earlier (Bendtsen et al. 1994).

*Methods*

The examination was performed in a standardized manner by the same investigator, a trained technician (HA), throughout the whole study. The subjects were examined sitting in a dental chair with headrest.

*Total tenderness*

Tenderness of specified pericranial regions was recorded according to the Total Tenderness Scoring system, which has previously proved to be reliable (Bendtsen et al. 1995a). Five pairs of muscles (masseter, temporal, frontal, sternocleidomastoid and trapezius muscles) and three pairs of tendon insertions (coronoid and mastoid processes and neck muscle insertions) were palpated. Palpation was performed with small rotating movements of the observer's second and third fingers. Pressure was sustained for 4-5 seconds. Prior to the study, the palpometer was used to train the observer to exert a palpation pressure of moderate intensity (140 U). The tenderness was scored on a 4-point (0-3) scale as follows: 0 = denial of tenderness, no visible reaction; 1 = verbal report of discomfort or mild pain, no visible reaction; 2 = verbal report of moderate pain,

with or without visible reaction; 3 = verbal report of marked pain and visible expression of discomfort. The values from left and right sides were summed to a Total Tenderness Score (maximum possible score = 48).

*Stimulus-response functions*

Stimulus-response functions for pressure versus pain were recorded during pressure-controlled palpation, i.e. palpation with controlled pressure intensity by means of the palpometer. Pressure-controlled palpation has previously proved to be a reliable method of tenderness recording (Bendtsen et al. 1995a). Palpation was performed with small rotating movements of the observer's second finger. Pressure was sustained for 4-5 seconds. The subjects were palpated at the trapezius and temporal muscles at the non-dominant side. These muscles have previously been found to represent a highly tender and a largely normal muscle respectively in patients with tension-type headache (Jensen et al. 1993b). Palpation was performed with seven different pressure intensities chosen in random order in the range from 80 to 200 U. At each pressure intensity the subject indicated the corresponding pain intensity on a visual analogue scale blinded for the observer. The visual analogue scale consisted of a 100-mm line with endpoints designated "no pain" and "unbearable pain". The degree of tenderness elicited in each subject was calculated as the area under the stimulus-response curve (AUC) according to the trapezium rule (Matthews et al. 1990).

*Statistics*

Results are presented as mean ± SE. Data were analyzed with Mann-Whitney's test and simple linear regression. Five percent was accepted as level of significance.

## RESULTS

*Total tenderness*

The Total Tenderness Score in patients was 17.7 ± 1.7 and significantly higher than 3.4 ± 0.53 in controls, $P<0.00001$.

*Stimulus-response functions*

The stimulus-response functions for pressure versus pain in the trapezius muscle in patients and in controls are shown in Figure 2. Calculating the area under the stimulus-response functions revealed that patients were significantly more tender (AUC=3370 ± 423 mmU) than controls (AUC=1693 ± 269 mmU), $P=0.002$. In controls, pain intensities increased in a positively accelerating fashion with increasing pressure intensities. The stimulus-response function was well described by a power function. This was demonstrated by obtaining an approximately linear relation between pressure and pain in a double logarithmic plot, slope

($\beta$)=3.8 ± 0.61 logmm/logU, P=0.002 (Figure 2, inset). In contrast, the stimulus-response function was approximately linear in patients, $\beta$=0.50 ± 0.04 mm/U, P=0.00004. Thus, the stimulus-response functions in controls and in patients were qualitatively different.

The stimulus-response functions for pressure versus pain in the temporal muscle are shown in Figure 3. Patients were slightly more tender (AUC=2139 ± 327 mmU) than controls (AUC=1722 ± 257 mmU), but the difference was not statistically significant, P=0.42. In controls, pain intensities increased in a positively accelerating fashion with increasing pressure intensities. In a double logarithmic plot the relation between pressure and pain was linear, $\beta$=6.7 ± 0.36 logmm/logU, P=0.00001 (Figure 3, inset). In patients, pain intensities increased in a positively accelerating fashion with increasing pressure intensities. However, the curve was irregular partly resembling a linear function. The regression function was approximately linear in a double logarithmic plot $\beta$=3.0 ± 0.36 logmm/logU, P=0.0002 (Figure 3, inset).

To explore whether the abnormal stimulus-response function in the trapezius muscle was related to the increased tenderness or to the diagnosis of tension-type headache, the patients were subgrouped on the basis of their degree of tenderness. The stimulus-response functions for the 20 most tender patients (AUC=5359 ± 538 mmU) and for the 20 least tender patients (AUC=1381 ± 176 mmU) are shown in Figure 4. In the 20 most tender patients, the stimulus-response function was linear, $\beta$=0.69 ± 0.03 mm/U, P<0.00001. In contrast, pain intensities increased in a positively accelerating fashion with increasing pressure intensities in the 20 least tender patients. In a double logarithmic plot the relation between pressure and pain was linear, $\beta$=4.0 ± 0.18 logmm/logU, P<0.00001 (because none of the patients reported any pain at the lowest stimulus intensity (U=80), a value of 1 mm was added to all pain intensities in order to perform this analysis)(Figure 4, inset).

## DISCUSSION

Possible physiological mechanisms leading to myofascial pain include: a) sensitization of peripheral myofascial nociceptors, b) sensitization of second order neurons at the spinal/trigeminal level, c) sensitization of supraspinal neurons, and d) decreased antinociceptive activity from supraspinal structures. These mechanisms may be investigated by relating the intensity of mechanical pressure applied to deep tissues to the response recorded from sensory neurons. Such studies on animal models have provided important information on deep tissue pain (Ness and Gebhart 1987; Cervero and Sann 1989; Yu and Mense 1990; Jänig and Koltzenburg 1991), but till now the relation between pressure and pain has not been investigated in patients with chronic myofascial pain.

Previously the stimulus-response function for pressure versus pain had been studied in 30 subjects with tender pericranial muscles (15 headache patients and 15 volunteers) (Bendtsen et al. 1995a). In the trapezius muscle, an approximately linear stimulus-response function virtually identical to the one recorded in patients in the present study was found. The finding of almost identical results in two different but comparable populations, obtained by two different observers, indicates that the employed method for recording of stimulus-response functions is reliable.

Before the present investigation, the stimulus-response function in normal muscle was expected by the inventors to be qualitatively similar to the stimulus-response function in tender muscle, i.e. linear, but with a less steep slope or with a parallel shift to the right as hypothesized by Jensen (Jensen 1990). Surprisingly, the relation between palpation pressure and pain in normal muscle and in highly tender muscle differed markedly. In the trapezius and temporal muscles of controls, pain intensities increased in a positively accelerating fashion with increasing pressure intensities, a relation that was well described by a power function. The same was found in patients in the temporal muscle which was only slightly to moderately tender. The patients were subgrouped on the basis of their degree of tenderness, the stimulus-response function was linear in the most tender patients, while it was well described by a power function in the least tender patients. Thus, the stimulus-response function becomes increasingly linear with increasing degrees of tenderness and the qualitatively changed stimulus-response function is related to actual tenderness and not to the diagnosis of tension-type headache. The possibility that the linear stimulus-response function was due to a shift to the left of the normal stimulus-response function such that the patients were on the steep part of the curve already at low pressures can be excluded. If so, the patients would have been much more tender than controls also at the lowest stimulus-intensities, which was not the case.

The present finding of a qualitatively altered response to nociceptor stimulation in tender muscle demonstrates for the first time that myofascial pain has a physiological basis and that myofascial pain, at least in part, is caused by qualitative changes in the processing of sensory information. These changes may be located to peripheral nerve endings, to the spinal cord or to higher order neurons.

Spinal dorsal horn neurons that receive input from deep myofascial tissues can be classified as high-threshold mechanosensitive (HTM) neurons requiring noxious intensities of stimulation for activation and as low-threshold mechanosensitive (LTM) neurons, which are activated by innocuous stimuli (Mense 1993). Yu and Mense (Yu and Mense 1990) have shown that HTM dorsal horn neurons have a positively accelerating stimulus-response function, whereas the stimulus-response function of LTM neurons is approximately linear. This indicates that the

linear stimulus-response function in tender human muscle may be caused by activity in LTM afferents. LTM afferents do not normally mediate pain, but strong input from peripheral nociceptors can remodel the circuitry of the dorsal horn by unmasking previously ineffective synapses and by forming novel synaptic contacts between LTM afferents and dorsal horn neurons that normally receive input from HTM afferents (Wall 1977; Wall and Woolf 1984; Cervero and Jänig 1992; Hu et al. 1992; Woolf et al. 1992; Mense 1993; McMahon et al. 1993; Mayer and Gebhart 1994; Hoheisel et al. 1994). In this way LTM afferents can mediate pain (Woolf and Thompson 1991). While the above-mentioned studies have been performed on animal models (Torebjörk et al. 1992). Torebjörk et al. have demonstrated similar changes in the central processing of inputs from LTM afferents in humans following intradermal injection of capsaicin. It therefore seems probable that the present findings can be explained by changes in neuronal behaviour at the spinal/trigeminal level. Support for this explanation was provided by a simultaneous investigation of pain thresholds in the same subjects by means of an electronic pressure algometer. Patients had significantly lower pressure pain detection and tolerance thresholds in fingers than controls (Bendtsen et al. 1996a). This indicates that the pain perception is centrally disturbed. A decrease of the supraspinal descending inhibition probably does not explain the present findings, because it has been reported that the descending inhibition acts via a parallel shift or via a decreased slope of the stimulus-response curve (Ness and Gebhart 1987; Yu and Mense 1990), while it does not change the shape of the stimulus-response curve. Sensitization of normally active peripheral nociceptors would probably induce a quantitative rather than a qualitative change of the stimulus-response curve (Koltzenburg et al. 1992).

The results thus demonstrate for the first time that nociceptive processes are qualitatively altered in patients with chronic tension-type headache, and that the central nervous system is sensitized at the spinal/trigeminal level in these patients.

**Recent studies from the present inventors indicating that the central sensitization is induced by prolonged muscle pain**

As mentioned above, the information obtained from basic pain research suggests that the central sensitization in chronic tension-type headache is induced and probably maintained by prolonged noxious input from the periphery. Prolonged muscle pain is, in particular, likely to induce central sensitization, because input from muscle nociceptors is more effective in inducing prolonged changes in the behaviour of dorsal horn neurons than is input from cutaneous nociceptors (Wall and Woolf 1984). Recent research from the present inventors does for the first time support that there is a clear relation between central pain sensitivity and the increased muscle pain in patients with tension-type headache, and that the increased central pain

sensitivity is induced by the increased muscle pain. Thus, it has recently been demonstrated that patients with chronic tension-type headache have decreased pain thresholds to various types of stimuli both at cephalic and at extra-cephalic locations (Bendtsen et al. 1996b), indicating a state of central hypersensitivity, and that there is a significant correlation between cephalic as well as extra-cephalic pain thresholds and the total pericranial tenderness recorded by manual palpation (Bendtsen et al. 1996a). These findings demonstrate that there is a close relationship between the increased pericranial tenderness and the central hypersensitivity in chronic tension-type headache, but it does not reveal the cause and effect relationship between these abnormalities. However, since it is known that patients with episodic tension-type headache have normal pain thresholds (Jensen et al. 1993b) and that chronic tension-type headache usually evolves from the episodic form (Langemark et al. 1988), and since experimentally induced tenderness of masticatory muscles precedes the induced headache by several hours in patients with tension-type headache (Jensen and Olesen 1996), it is most likely that increased myofascial tenderness precedes central hypersensitivity.

## EXAMPLE 2

MECHANISMS OF SPONTANEOUS TENSION-TYPE HEADACHES.
- An analysis of tenderness, pain thresholds and EMG

Pericranial muscle tenderness, EMG-levels and thermal and mechanical pain thresholds were studied in 28 patients with tension-type headache and in 30 healthy controls. Each patient was studied during as well as outside a spontaneous episode of tension-type headache. Outside of headache muscle tenderness and EMG-levels were significantly increased compared to values in controls subjects, while mechanical and thermal pain thresholds were largely normal. During headache muscle tenderness evaluated by blinded manual palpation increased significantly, while pressure pain thresholds remained normal and pressure pain tolerances decreased. Thermal pain detection and tolerance threshold decreased significantly in the temporal region, but remained normal in the hand. EMG-levels were unchanged during headache. The findings indicate that one of the primary sources of pain in tension-type headache may be a local and reversible sensitization of nociceptors in the pericranial muscles. In addition, a segmental central sensitization may contribute to the pain in frequent sufferers of tension-type headache. The present study, for the first time, examines the same patients both during headache and outside of a headache episode with the following tests: EMG, pericranial palpation, mechanical and thermal pain thresolds. The aim was to analyze the relative importance of central and peripheral nociceptive factors.

## SUBJECT AND METHODS

*Subjects*

Twenty eight patients, 11 males and 17 females, with frequent episodic or chronic tension-type headache fulfilling the IHS-criteria (HCCIHS 1988) were included (Table IV). The patients were recruited from the out-patient headache clinic at Gentofte Hospital, Denmark. 9 patients with frequent episodic tension-type headache(ETH) ≥ 8 days per month and 19 patients with chronic, but not daily, tension-type headache (CTH) (HCCIHS 1988) were included. The reason for this selection was that patients had to have frequent headaches as well as frequent days without headache in order to be studied in both states. Further inclusion criteria were frequent headaches during at least one year and an age between 18 and 70 years. The exclusion criteria were: Daily headache, migraine more than 1 day per month, cluster headache or trigeminal neuralgia, other neurological, somatic or psychiatric disorders, concurrent ingestion of major medications including migraine prophylactics, any form of drug abuse or dependency including large amounts of plain analgesics. A diagnostic headache diary had to be filled out during a 4 week run-in period to ensure that patients fulfilled the inclusion criteria. A complete physical and neurological examination was performed before entry. Thirty age- and sex-matched healthy subjects without tension-type headache( < 14 days TH/year) were used as controls (Table IV). Informed consent was obtained and the study was approved by the local ethical committee.

*Methods*

The patients were examined randomly during and outside a typical episode of tension-type headache. The intensity of the headache was recorded initially on a 100 mm Visual Analogue Scale(VAS), where 0 indicated no pain at all and 100 mm indicated the worst imaginable pain. Examinations were separated by at least one week and performed at the same time of the day in order to eliminate diurnal variations. Patients were not allowed to take any medication on the days of examination. Healthy controls were investigated once.

*Examination*

The examination was performed in a standardized fashion by the same investigator, a trained technician(LH), throughout the whole study. The technician was blinded to the subjects' headache history and presence or absence of a possible muscular factor. Before measuring pain thresholds each individual was carefully instructed to apply the same interpretation of 'painful' throughout the study. Initial test sessions were applied to all subjects in order to familiarize them with the test conditions.

*Palpation method*

Pericranial tenderness was evaluated by palpation of 9 pairs of muscles and tendon insertions in a standardized way. Each patient was examined by the technician and the physician in random order. Tenderness was scored at each location according to a four point scale from 0 to 3, and scores from all sites were summated. The maximally possible score was thus 54 points. This Total Tenderness Score system (TTS) has previously proved to be reliable (Bendtsen et al. 1996).

*Pressure Pain Threshold*

The mechanical pain thresholds and tolerances were evaluated bilaterally on the distal dorsal part of the second finger. Similarly, 2 cranial locations, one with interposed muscle, the anterior part of the temporal muscle (temp) and one without interposed muscle, the parietal region (par) were examined (Petersen et al. 1992). A standardized and previously evaluated method was applied using an electronic pressure algometer (Somedic AB, Sweden) with a 0.79cm$^2$ circular probe (Jensen et al. 1986, Brennum et al. 1989). The Pressure Pain Detection Threshold (PPDT) was defined as the threshold, where the pressure sensation became painful, whereas the Pressure Pain Tolerance (PPTO) was the threshold where the patient would no longer tolerate the pain (Petersen et al. 1992). By pressing a hand-held button the subjects indicated that the pain threshold was reached and the pressure was immediately released. If patients did not activate the button, the experiment was terminated when reaching 800 kPa in the cranial region and 1500 kPa in the fingers. Each threshold was calculated as the median value of 3 consecutive recordings.

*Thermal thresholds*

Thermal thresholds were evaluated with a computerized version of the Thermotest (Somedic AB, Sweden)(Fruhstorfer et al. 1976). The thermode consisted of series-coupled Peltier elements and measured 25x50 mm. Two locations, the thenar region of the hand and the anterior part of the temple were examined bilaterally. Three parameters were recorded in each region i.e. the Warm Detection (WD) defined as the lowest temperature detected as warm, the Heat Pain Detection (HPD) defined as the temperature where the heat sensation became painful, and the Heat Pain Tolerance(HPTO) defined as the highest temperature tolerated (Langemark et al. 1989, Jamal et al. 1985). A baseline temperature of 32$^o$ C and a 1.0$^o$ C /sec rate of temperature change was used (Langemark et al. 1989). Heat stimulation was terminated when reaching 52 $^o$ C if the patients had not responded before. By pressing a hand-held button the subjects indicated, when the thresholds were reached. The thermode was immediately removed from the area, the exact value was recorded in the computer and the stimulator returned to baseline. Each threshold was calculated as the average of 5 determinations performed with intervals of 10-15 seconds.

*Electromyography*

A standardized, previously described method was used (Jensen et al. 1993a, Jensen et al. 1994). The EMG signals from the temporal and trapezius muscles were recorded bilaterally using a 4-channels electromyograph (Counterpoint, Dantec, Copenhagen). Data were collected during 2 conditions i.e. resting in the supine position in 20 one second periods interrupted by 5 second interval and during maximal voluntary contraction (MVC). The MVC lasted a maximum of 5 seconds and was repeated 5-6 times with 30 second intervals. MVC recording sessions lasting one second were analyzed and the highest value of Root Mean Square (RMS) of the EMG was selected (Jensen et al. 1993a, Jensen et al. 1994). The power spectrum of each of the 1 second measurement sessions was calculated for the frequency range 0 to 1 kHz and Mean Frequency was extracted (Jensen et al. 1993a).

## STATISTICS

Wilcoxons rank sum test(Wilc.) was used to compare paired data from headache subjects. Mann-Whitneys test(M-W.) was used to compare data between controls and patients. Mean values of right and left sided observations are presented. Five per cent level of significance was used.

## RESULTS

*Subjects*

All the included patients and healthy controls completed the study. There were no significant differences in age and sex-distribution between healthy subjects and patients (Table IV).

*Headache*

The headaches examined fulfilled the diagnostic criteria for tension-type headache (HCCIHS 1988). Seventy one percent (20/28) had a bilateral headache, whereas 29%(8/28) had a unilateral headache. The median VAS score was initially 35 mm (range 17-75 mm).

*Variation between observers*

The Total Tenderness Scores(TTS) as recorded by the 2 observers (LH, RJ) at the initial examination were comparable in patients (Wilc. $p=0.38$) and in healthy controls (Wilc. $p=0.27$).

*Side to side relation*

The side to side variations were tested in patients as well as in controls, and results corresponded to previous methodological studies (Petersen et al. 1992, Jensen et al. 1986, Jamal et al. 1985, Jensen et al. 1993a).

**Relation between controls and patients free of headache**

*Tenderness*

Median TTS in TH patients free of headache was 13 and significantly higher than 4 in healthy controls

(M-W.$p < 10^{-5}$) (Fig.6).

*Pressure pain thresholds*

Pressure Pain Detection Thresholds and Pain Tolerance Thresholds in patients were not significantly different from those in healthy controls in any of the examined regions (Table V).

*Thermal thresholds*

The warm detection threshold, the heat pain detection and tolerance thresholds in the hands did not differ between patients and controls. In the temporal regions of headache free patients the warm detection (WD) and heat pain thresholds (HPD) were increased compared to healthy controls (Table VI) (M-W. WD:$p < 0.001$;HPD:$p = 0.047$). The heat pain tolerances were similar in the 2 groups (Table VI).

*EMG*

During rest amplitude-levels were higher in patients in the headache free condition as compared to healthy controls (M-W. m.temp:$p < 0.001$;m.trap $p = 0.016$). No other significant differences or tendencies were detected (Table VII).

**Relation to the headache state**

*Tenderness*

The total tenderness score increased from 13 (range 0-29) outside of headache to 16 (range 1-34) during headache (Wilc.$p < 0.01$) (Fig.6)

*Pressure pain thresholds*

No significant differences in pressure pain detection thresholds were found when results during headache were compared to the headache free condition. Pressure pain tolerances in the parietal regions decreased significantly during the headache (Wilc. $p = 0.03$), whereas the pressure pain tolerances from other locations were unaffected (Fig.7).

*Thermal thresholds*

Heat pain detection (Wilc.p=0.011) and tolerances (Wilc.p=0.016) were lower in the temporal region during headache as compared to the headache free condition. No differences were seen in the hand (Fig.8).

*EMG*

No significant variations appeared when EMG parameters during the headache episode were compared to the headache free condition (Fig.8 A+B).

## DISCUSSION

### Comparison of headache-free patients and control subjects

Myofascial tissue has been considered an important source of nociception in tension-type headache by some investigators (Travell et al. 1983, Drummond et al. 1987), whereas others favor alterations in central pain processing resulting in a state of hypersensitivity to incoming stimuli from myofascial and other cephalic tissues (Schoenen et al. 1991a, Schoenen et al. 1991b). Previous findings of increased cranial and peripheral sensitivity in patients with chronic tension-type headache support such central mechanisms (Langemark et al. 1989, Schoenen et al. 1991b). However, normal cranial pressure pain thresholds have recently been described in subjects with chronic tension-type headache from a general population (Jensen et al. 1993b) and in patients with episodic tension-type headache from headache clinics (Goebel et al. 1992, Bovim et al. 1992). Comparing groups of headache patients to normal controls involves many confounding factors. These are greatly diminished in studies comparing the headache state and the non-headache state in the same individuals. The same patients were studied both during and outside of headache. The headache mechanisms were analyzed by means of EMG, peri-cranial palpation, thermal and mechanical pain sensitivity.

The present study confirms that pericranial muscles of these patients outside of headache are more tender than in healthy subjects (Jensen et al. 1993, Hatch et al. 1992, Langemark et al. 1987). More importantly it is demonstrated, for the first time, that tenderness increases during the headache phase. Are these findings due to central or peripheral hypersensitivity? Normal pressure pain thresholds and pressure pain tolerances outside headache both in the cranial region and in the hands indicates that central pain perception is not generally affected in these patients. The warm detection and heat pain detection thresholds were increased, not decreased, in the temporal region and normal in the hands. Thus, decreased sensitivity to noxious heat can be due to either a local factor in the skin which decreases the cutaneous receptor sensitivity or central factors inhibiting the incoming stimuli. No studies have addressed this issue before and

the finding needs further clarification. Higher EMG-amplitude values during rest were recorded in headache free patients as compared to normal controls. These findings correspond with a recent population study where amplitude levels from the temporal and the frontal muscles were increased in subjects with chronic tension-type headache (Jensen et al. 1994). These findings indicate that the muscles are insufficiently relaxed. Whether this is causative or secondary to the headache has been much debated, but lack of correlation to the pain state(see below) indicates that it may be a secondary characteristic. In the study presented in example 3 it is described that sustained tooth clenching may be an initiating event of tension-type headache, but the present results suggests that other mechanisms are responsible for maintaining it.

**Relation to the headache state**

During headache pericranial tenderness increased, indicating peripheral or central sensitization of myofascial nociception (Jensen et al 1990). EMG-levels were unchanged during headache which makes it unlikely that pain elicited activity in pericranial muscles can explain the increased tenderness. Pressure pain thresholds were unaffected by the headache state whereas thermal pain detection and tolerance thresholds decreased selectively in the temporal region indicating that the actual headache episode may be associated with a segmental central sensitization and/or a decreased antinociception. A more generally defective central pain modulation, as previously suggested (Schoenen et a. 1991a), is less likely, because pressure pain thresholds and tolerances in the hands were completely normal. A possible segmental disturbance at the spinal/trigeminal level may be transient and reversible since pain tolerances were normal outside of headache. The results are thus in line with the recent experimental studies by Hu et al.(Hu et al. 1992). In these important studies deep craniofacial muscle afferents were stimulated and prolonged facilitatory effects in the trigeminal nociceptive brain-stem neurons of anaesthetized rats were induced. These findings were supported by the recent findings that experimental myositis induces functional reorganization of the rat dorsal horn (Hoheisel et al. 1994). A reversible expansion of the cutaneous mechanoreceptive field was noted by Hu et al. and the spontaneous activity in cutaneous afferents was increased (Hu et al. 1992) in correspondence with previous studies (Coderre et al. 1993, Heppelmann et al. 1987). It is also known that input from deep myofascial tissue is more effective in inducing central sensitization than cutaneous input (Wall et al. 1984, Yu et al. 1993),

The decreased pain tolerances during headache in the present study may indicate a central hyperalgesia. As pain tolerances were normal outside of headache, the central changes are probably reversibly linked to the headache pain in the episodic form, whereas a more frequent activation may induce a permanent pain condition, i.e. the chronic form, The cascade of increased nociceptive activity from deep myofascial tissues may induce secondary changes such

as plasticity and sensitization in the spinal dorsal horn/trigeminal nucleus (Hu et al. 1992, Hogeisel et al. 1994, Coderre et al. 1993, Heppelmann et al. 1987). The central nociceptive modulation and perception are thereby disturbed resulting in a prolonged hyperalgesia, which may persist despite disappearance of the peripheral noxious stimulus. When the central sensitization becomes sufficiently strong and widespread, the headache becomes chronic due to self perpetuating disturbances in the pain perception system.

Many of the abnormal findings in previous series of severely affected patients with chronic tension-type headache (Schoenen et al. 1991a, Langemark et al. 1989, Schoenen et al. 1991b) may be a function of the pain rather than the initial causative factor. It can therefore be recommended to study mechanisms in patients with episodic tension-type headache. Studies comparing the pain state to the pain free state in these patients are likely to be the most informative.

TABLE IV

Clinical characteristics of the subjects studied

| | TH patients | Controls |
|---|---|---|
| Number (n) | 28 | 30 |
| Males | 11 | 12 |
| Females | 17 | 18 |
| Age(years) | 45(28-63) | 42(23-67) |
| Years with TH | 23(1-45) | - |
| Frequency of TH days/28 days | 20(8-27) | - |
| Frequency of migr days/year (n=14) | 8(2-11) | - |

Mean values with range in brackets are given

TABLE V

Pressure pain thresholds in 28 headache patients free of headache and 30 healthy controls. Mean values of left and right side are given in kPa with SD in brackets.

| | Pressure pain detection | Pressure pain tolerance |
|---|---|---|
| patients | 384(161) | 739(271) |
| HANDS | | |
| controls | 358(168) | 785(289) |
| patients | 225(97) | 366(141) |
| TEMPORAL REG. | | |
| controls | 203(103) | 387(157) |
| patients | 339(172) | 560(179) |
| PARIETAL REG. | | |
| controls | 317(194) | 571(201) |

No significant differences between patients and controls.

TABLE VI

Thermal thresholds in 28 headache patients free of headache and 30 healthy controls. Mean values of left and right side are given in $^{o}C$ with SD in brackets.

| | Warm Detection | Pain threshold | Pain tolerance |
|---|---|---|---|
| patients | 34.3 (3.1) | 42.3 (3.1) | 47.0 (2.2) |
| HANDS | | | |
| controls | 34.4 (1.2) | 42.4 (2.7) | 47.5 (2.2) |
| patients | ***34.7 (1.6) | *40.1 (2.8) | 44.1 (2.0) |
| TEMP | | | |
| controls | 33.8 (0.8) | 39.1 (2.7) | 43.9 (8.5) |

* $p < 0.05$
*** $p < 0.001$
(Mann- Whitney´s test)

TABLE VII

EMG levels in 28 patients free of headache and in 30 healthy controls. REST indicate resting conditions and MVC indicate maximal voluntary contraction. Mean values of left and right side are given with SD in brackets.

| | REST | | MVC | |
|---|---|---|---|---|
| | RMS (uV) | Mean F (Hz) | RMS (uV) | Mean F (Hz) |
| TEMPORAL MUSCLES | | | | |
| patients | **3.1 (2.4) | 81 (25) | 164 (66) | 173 (28) |
| controls | 2.3 (0.9) | 74 (17) | 181 (101) | 155 (30) |
| TRAPEZIUS MUSCLES | | | | |
| patients | *3.6 (1.2) | 40 (10) | 260 (141) | 88 (18) |
| controls | 3.1 (0.9) | 41 (9) | 259 (131) | 88 (16) |

* $p<0.05$
** $p<0.01$
(Mann- Whitney´s test)

## EXAMPLE 3

### INITIATING MECHANISMS OF EXPERIMENTALLY INDUCED TENSION-TYPE HEADACHE

To elucidate possible myofascial mechanisms of tension-type headache, the effect of 30 minutes of sustained tooth clenching (10% of maximal EMG-signal) was studied in 58 patients with tension-type headache and in 30 age and sex matched controls. Pericranial tenderness, mechanical and thermal pain detection and tolerance thresholds and EMG levels were recorded before and after the clenching procedure. Within 24 hours 69% of patients and 17% of controls developed a tension-type headache. Shortly after clenching, tenderness was increased in the group who subsequently developed headache, whereas tenderness was stable in the group of patients who remained headache free. Mechanical pain thresholds evaluated by pressure algometry remained unchanged in the group which developed headache, whereas thresholds increased in the group which did not develop headache. Thermal pain detection and tolerance thresholds remained unchanged in both groups. These findings indicate that, although there may be several different mechanisms of tension-type headache, one of them is sustained muscle contraction. A peripheral mechanism of tension-type headache is therefore possible, whereas a secondary segmental central sensitization seems to be involved in subjects with frequent tension-type headache. Finally, the increase in pressure pain thresholds in patients who did not develop headache suggest that clenching activated their antinociceptive system whereas those developing headache were unable to do so.

### INTRODUCTION

Tension-type headache is extremely prevalent (Rasmussen et al. 1991) and represents a major health problem (Rasmussen et al. 1992). Nevertheless, its pathogenic mechanisms are largely unknown (Pikoff et al. 1984, Olesen et al. 1991). Sustained involuntary muscle contraction has been suggested as an important source of pain in tension-type headache (Travell et al. 1983). In recent years, central mechanisms have however, been favoured (Schoenen et al. 1991a). Substantial evidence for any of the suggested pathogenetic mechanisms has not yet been available. To study the initiating mechanisms of headache it is valuable to induce it. The time necessary to reach the laboratory makes it impossible to study the initial phase of spontaneous attacks. Furthermore, using a known stimulus to induce headache makes it easier to analyze its mechanisms. Experimental tooth clenching has previously induced mild headaches in migraineurs (Jensen et al. 1985) but has never been studied in subjects with tension-type

headache. In the present study tension-type headache was induced by sustained muscle contraction in patients and controls and studied the pre- and post-contraction phase by means of EMG, thermal and pressure pain thresholds as well as headache and tenderness scoring.

## SUBJECTS AND METHODS

*Subjects*

Fifty-eight patients with frequent episodic or chronic tension-type headache fulfilling the IHS-criteria (HCCIHS 1988) were included (Table VIII). Twenty eight patients had frequent episodic tension-type headache ≥8 days with headache per month and 30 patients had chronic, but not daily, tension-type headache (HCCIHS 1988). The reason for this selection was that patients had to have frequent headaches as well as days without headache in order to be studied in the latter state. Further inclusion criteria were duration of frequent tension-type headache in at least one year and age between 18 and 70 years. The exclusion criteria were: daily headache, migraine more than 1 day per month, cluster headache, trigeminal neuralgia, other neurological, systemic or psychiatric disorders, ingestion of major medications including migraine prophylactics, any form of drug abuse or dependency as daily ergotamine or large amounts of plain analgesics. The patients were recruited from the out-patient headache clinic at Gentofte Hospital and complete physical and neurological examinations were done before entry. Thirty healthy age- and sex matched subjects (headache <14 days /year) were used as controls (Table VIII). Informed consent was obtained and the study was approved by the local ethical committee.

*Procedure*

All patients had to fill in a diagnostic headache diary during a 4 week run-in period to ensure that patients fulfilled the inclusion criteria. All subjects, patients and controls, were told to fill out a special diary for at least 24 hours after the study. Patients were examined when free of headache and were not allowed to have taken any analgesics on the day of examination. The EMG-parameters and pain characteristics were recorded twice on the day of examination, immediately before and after the clenching procedure. A 100 mm Visual Analogue Scale (VAS), where 0 mm was no pain at all and 100 mm was the worst imaginable pain was used. Recordings of pain intensity were made before, 30, 60 and 90 minutes after the clenching procedure in the laboratory, as well as after 4, 6, and 24 hours after the clenching in the diary. All subjects were informed that the purpose of the study was to measure variations in muscle tension and pain characteristics during tooth clenching. They were not informed of the risk of developing headache in order to avoid bias.

*Examination*

The examination was performed in a standardized way by the same person, a trained technician, throughout the whole study. The study was blinded as the technician was unaware of the subjects' headache history. Before recordings of pain thresholds each individual was carefully instructed to apply the same interpretation of 'painful' throughout the study. Initial test sessions were applied to all subjects in order to familiarize them with the test conditions.

*Palpation*

Pericranial tenderness was evaluated by palpation of 9 pairs of muscles and tendon insertions by the technician and the physician in a standardized, randomized procedure. Tenderness was scored in each location according to an ordinal scale from 0 to 3, and scores from all sites were summated. The maximum possible score was thus 54 points. This Total Tenderness Score system (TTS) has previous proved to be reliable (Bendtsen et al. 1995).

*Pressure Pain Thresholds*

The pressure pain thresholds were evaluated bilaterally on the distal dorsal part of the second finger, and in two cranial locations, one with interposed temporal muscle (Temp) and one without interposed muscle, the parietal region (Par). A standardized and previously evaluated method was applied using an electronic pressure algometer (Somedic AB, Sweden) with an 0.79 $cm^2$ circular stimulation probe (Petersen et al. 1992, Jensen et al. 1986, Brennum et al. 1989). Two pain qualities were recorded, the Pressure Pain Detection Threshold (PPDT) defined as the threshold, where the pressure sensation became painful, and the Pressure Pain Tolerance (PPTO) defined as the threshold where the patient would no longer tolerate the pain (Petersen et al. 1992). By pressing a hand held button the subjects indicated that the threshold was reached, and the pressure was released immediately. If patients did not activate the button, the experiment was terminated when reaching 800 kPa in the cranial region and 1500 kPa in the fingers. Each threshold was calculated as the median value of 3 determinations performed with intervals of 10-15 seconds.

*Thermal Pain Thresholds*

Thermal thresholds were evaluated with a computerized version of the Thermotest (Somedic AB, Sweden)(Fruhstorfer et al. 1976). The thermode consisted of series-coupled Peltier elements and measured 25x50 mm. The thenar region of the hand and the anterior part of the temporal region were examined bilaterally. Three stimulation qualities were recorded; the Warm Detection limit (WD) defined as the lowest temperature detected as warm, the Heat Pain Detection (HPD) defined as the temperature where the heat sensation became painful, and the Heat Pain Tolerance (HPTO) defined as the highest temperature tolerated (Jamal et al. 1985). A baseline temperature of 32 °C and a 1.0 °C/sec rate of temperature change was used. Heat

stimulation was terminated when reaching 52 °C, if the patients had not responded before. By pressing a hand-held button the subjects indicated when the actual threshold was reached. This value was recorded automatically and the stimulator returned to baseline. Each threshold was calculated as the average of 5 determinations performed with intervals of 10-15 seconds.

*Electromyography*

EMG signals from the temporal and trapezius muscles were recorded bilaterally by a 4-channels electromyograph (Counterpoint, Dantec, Copenhagen)(Jensen et al. 1993a). A standardized, previously described method where the temporal and frontal muscles were investigated were applied (Jensen et al. 1993a). Data were collected during rest in the supine position and during maximal voluntary contractions (MVC) (Jensen et al. 1993a). The RMS voltage was measured. Power spectrum was calculated for the frequency range 0 to 1 kHz and Mean Frequencies (Mean F) were extracted (Jensen et al. 1993a).

*Provocation*

After the initial recording series the subjects were instructed to clench their molar teeth and the EMG activity from the temporal muscles was recorded. The subjects were instructed to clench their teeth at 10% of their individual MVC value and to keep this value constant for 30 minutes. The subjects received visual feed back from the EMG-monitor, and were allowed 3 short (< 60 sec) rests during the session. Force was not measured.

## STATISTICS

The chi square test was used to test differences in headache characteristics between patients and controls. The sign test was used to compare the frequency of provoked headache with the expected frequency. Wilcoxon's rank sum test (Wilc.) was used for comparing paired data within subjects, and Mann-Whitney's test (M-W.) was used for comparing unpaired data between patients and controls. Five per cent level of significance was used.

## RESULTS

All the included patients and healthy controls completed the study. No significant variation in age- and sex distribution between patients and controls appeared (Table VIII). Only two left handed subjects (1 patient, 1 control) were included. Therefore no correction for hand dominance was made.

**Development of headache**

In total, 69%(40/58) of the patients and 17%(5/30) of the healthy controls developed headache within 24 hours after tooth clenching. The frequency of headache among patients was significantly higher than expected from their usual headache frequency($p=0.016$) and higher than in healthy controls ($p<0.0001$). Twenty-eight percent of patients(16/58) and 7% of controls(2/30) developed headache within the first hour after tooth clenching. The median duration from clenching to development of headache was 1.5 hours in patients (range 0.5-20 hours) and 1.5 hours (range 0.5-6 hours) in controls. All headaches, in patients as well as in controls, fulfilled the diagnostic criteria for tension-type headache(7). The headaches were bilaterally located in 85%(34/40) of the patients and in all controls. It was of pressing quality in all subjects. It was not aggravated by physical activity in 85%(34/40) of the patients and in all the controls. No associated symptoms such as nausea, photophobia or phonophobia were reported. Initially, the headache was very mild in both groups, but the intensity increased during the following hours in patients (Fig. 10). Four and 24 hours after clenching those patients who had developed headache had significantly higher mean VAS-scores than those few healthy controls who had developed headache (M-W. $p=0.02$)(Fig.10). In patients, the median headache duration was 8 hours (range 1-24 hours) but not significantly different from 3 hours (range 2-24 hours)(M-W. $p=0.10$) in the small number of controls($n=5$) with headache.

**Variation between observers**

The Total Tenderness Scores (TTS) recorded by the 2 observers at the initial examination did not differ significantly within patients (Wilc. $p=0.24$) nor in healthy controls (Wilc. $p=0.27$).

**Variation between left and right sided observations**

The side to side variations were tested in patients as well as in controls, and results corresponded to previous methodological studies (Petersen et al. 1992, Fruhstorfer et al. 1976, Jensen et al. 1993a, Jensen et al. 1993b). For simplicity mean values of left and right sided observations are presented in the following.

**Relation between measurements in patients and controls before clenching**

*Tenderness*

Initial median TTS in patients was 12 (range 0-29) and significantly higher than the median score of 4 (range 0-10) in healthy controls (M-W.$p<10^{-7}$).

*Pressure pain thresholds*

Pressure Pain Detection Thresholds were increased in the temporal regions of headache patients compared with healthy controls (M-W.p=0.03) (Table IX). No significant variations or tendencies were found in the other locations (M-W.fingers p=0.98; parietal p=0.21)(Table IX).

Pressure Pain Tolerances in patients were not significantly different from those in healthy controls in any of the examined regions (M-W.fingers p=0.87; temp. p=0.45; parietal p=0.69) (Table IX).

*Thermal thresholds*

The warm detection threshold was higher in the temporal regions in patients than in healthy controls (M-W. p=0.02), while the warm detection in the hands was normal (M-W. p=0.26)(Table X). The heat pain detection and tolerance thresholds were normal in both locations (Table X).

*EMG*

During rest the EMG-amplitude was significantly increased in the trapezius muscle of patients compared to controls (M-W.

Trap p=0.04). A similar but not quite significant increase was seen in the temporal muscles (M-W.Temp p=0.10)(Table XI). Frequency values during rest as well as all EMG values during MVC were not different from those of controls (Table XI).

**Effect of clenching on the measured tests**

*Tenderness*

The median initial TTS was 12 (range 0-28) in patients who developed headache and was increased significantly to 14 (range 0-33) at the recording 90 minutes after clenching (Wilc.p<0.001) (Fig.11). The median TTS in patients who remained headache free was also 12 (range 0-24) and remained 12 (range 0-33) after clenching (Wilc.p=0.83). A marked, but not quite significant increase in TTS from 6 to 10 was seen in the few control subjects who developed headache (Wilc.p=0.06), whereas TTS only increased from 4 to 5 in controls who remained headache free (Wilc.p=0.0015)(Fig.11).

*Pressure pain thresholds*

Pressure Pain Detection Thresholds in fingers and in the temporal regions remained constant in those subjects (patients as well as controls) who developed headache, whereas a significant increase of pain detection thresholds was seen in subjects who did not develop headache (Wilc. Patients fingers p=0.01;temp p=0.024; Controls fingers p=0.04;temp p=0.01)(Fig.12A).

Pressure Pain Tolerance decreased in the parietal region in patients who developed headache after clenching (Wilc.p=0.009), whereas the tolerances remained stable in patients who remained headache free. Pressure Pain Tolerances in the same region increased in controls who remained headache free after stimulation (Wilc.p=0.003)(Fig.12B). Pressure Pain Tolerance was stable in the hand and the temporal region in all subjects without regard to headache development(Fig.12B).

*Thermal thresholds*

In patients as well as in controls, no significant differences in thermal thresholds were seen between those, who developed headache and those who did not(Fig.13).

*EMG*

During resting condition a significant decrease in amplitude value was seen in the temporal and the trapezius muscles after clenching both in patients (Wilc.Temp. $p<0.001$, Trap. $p<0.01$) and in controls (Wilc. Temp.$p<0.001$, Trap. $p<0.01$). This decrease was similar in those who developed headache and in those who did not (Fig.14A). In contrast, only the group of patients who developed headache showed decreased amplitude values in the temporal muscle during MVC (Wilc. $p=0.011$)(Fig.14B).

## DISCUSSION

Studies in a general population and in specialized headache clinics have revealed that increased muscle tenderness and frequent tooth clenching are consistent findings in subjects with tension-type headache (Jensen et al. 1993b, Jensen et al. in prep., Wanmann et al. 1986, Langemark et al. 1987, Lous et al. 1982). Whether these relations are causal or secondary to the pain has not yet been clarified. However, if there is a causal connection it should be possible to create an experimental headache model by interfering with these systems. Although several attempts to make experimental pain in the chewing muscles have been made (Christensen et a. 1981, Clark et al. 1991, Bakke et al. 1989), only few studies have focused specifically on headache (Jensen et al. 1985, Magnusson et al. 1984). Jensen et al. reported that 54% of 48 migraineurs developed a muscle-contraction like headache after shortlasting sustained clenching (Jensen et al. 1985). These findings indicate that headache subjects in general are more susceptible to develop headache after sustained muscle contraction.

**Relation between measurements in patients and controls before clenching**

*Tenderness*

The finding of increased muscle tenderness by manual palpation as the most significant difference between headache patients and healthy controls supports previous findings in a general population (Jensen et al. 1993b). When selecting psycho-physiological measures it is important to consider the information carried by the particular measure. Local tenderness as recorded by manual palpation is assumed to indicate increased nociception from the free nerve endings in the connective tissue of muscles, fascia and tendons (Jensen et al. 1990, Torebjørk et al. 1984). Such increased nociception is probably due to a sensitization of nociceptors by bradykinin, prostaglandines, substance P, 5-HT, histamine and potassiu (Mense et al. 1992, Jensen et al. 1992). Reduced muscle blood flow leading to ischemia has been suggested as the cause of tenderness (Myers et al. 1983), but recently normal blood flow in the temporal muscles of patients with chronic tension-type headache has been demonstrated (Langemark et al. 1990).

*Pressure Pain Thresholds*

A decreased pressure pain detection threshold indicates a state of allodynia, i.e. pain elicited by stimuli which normally are non-noxious. A decrease in pressure pain tolerance threshold indicates a state of hyperalgesia,i.e. increased sensitivity for suprathreshold noxious stimuli, which may and may not coexist with allodynia (Jensen et al. 1990). Identification of allodynia and hyperalgesia may therefore be of special interest in the study of central and peripheral mechanisms of nociception. In addition, we have studied responses from the hands and the cranial regions in order to determine a possible anatomical variation in the response to pain stimulation. We also wanted to study the muscular contribution and recorded thresholds from two neighbouring cranial regions one with and one without interposed muscle. The fact that pressure pain detection thresholds and tolerances were lower in the temporal region than in the nearby parietal region indicates that myofascial nociception contributes considerably to the recorded responses. However, the finding of largely normal thresholds and tolerances in headache free patients indicates that the general pain sensitivity in the cranial region is not permanently disturbed as previously suggested (Schoen et al.,1991a, Langemark et al. 1989).

*Thermal thresholds*

Thermal warm detection represents the activity in unmyelinated C-fibers (Campbell et al. 1989) whereas the heat pain detection represents activation of cutaneous C-fibers responsive to mechanical and heat stimuli and their central modulation (Campbell et al. 1989). In addition, the myelinated A mechano heat fibers type I may be activated when the heat pain tolerance is tested. If central pain perception is increased, decreased warmth and heat pain thresholds are expected. However, thermal pain detection and tolerances were normal in the headache patients

suggesting normal pain sensitivity as discussed above. The present findings differ from a previous finding of decreased heat pain detection thresholds in patients with chronic tension-type headache (Langemark et al. 1989). In the prior study patients were, however, more severely affected and most of them had daily headaches and long lasting drug overuse (Langemark et al. 1989). It is likely that chronic pain may induce central sensitization to incoming nociceptive signals, and the previously described decrease in noxious thresholds in severely affected headache patients may, therefore, be an effect of chronic pain rather than its cause.

*EMG*

It has been a widely held view that tension-type headache is caused by involuntary contraction of cranial muscles. The slightly increased amplitude values during rest indicate that the pericranial muscles are insufficiently relaxed (Jensen et al. 1994). However, this increase in EMG level was unaffected by the presence or absence of headache, and is therefore not likely to be a primary cause of pain (Jensen et al. 1994). The decreased amplitude values during maximal voluntary contraction in patients developing headache and not in controls indicate that in some other way a muscular factor may be involved (Jensen et al. 1994).

**Effect of clenching on headache and the measured tests**

The present results indicate that sustained muscle contraction can induce headache although the recordings have not been repeated during a similar placebo provocation. An important finding is the increased tenderness in subjects who developed headache. Headache had not developed in the majority of subjects at 90 minutes after provocation, when the increased tenderness was recorded. This suggests that clenching causes tenderness, that tenderness precedes headache and that tenderness may be one of the causes of the subsequent headache. A similar increase in tenderness scores during spontaneous attacks of tension-type headache has recently been shown (Jensen et al. in press). Muscle tenderness usually requires several hours to develop (Christensen et al. 1981). A further increase in tenderness would therefore probably have been detected if we had continued to record tenderness several hours after clenching. In the present study, the experimental headache occurred with a lag time of one to several hours. In addition, the pain was mild initially and gradually, in the course of hours, reached its peak. In contrast, the intensity of headache in control subjects did not increase after onset. The very low VAS-score in controls may represent discomfort rather than clinical relevant pain as reported by the patients. This indicates that the antinociceptive system may be deficient in headache patients. The exact degree of clenching seems to be of minor importance. Approximately the same percentage of subjects developed headache with 10% of maximal contraction in the present study and with 5% or 30% of maximal contraction in the previous migraine study (Jensen et al. 1985).

**Mechanisms of tension-type headache suggested by the present results**

The pressure pain detection thresholds remained stable in patients who developed headache but increased in subjects who did not develop headache. We also found decreased pain tolerances in patients who developed headache, unchanged values in the remaining patients and increased values in controls, suggesting that headache patients do not activate their antinociceptive system or that it is less effective in these patients (Le Bars et al. 1979). On the other hand, their central antinociceptive suppression is not so permanently and severely affected that it is reflected in permanent hyperalgesia, since the noxious thresholds and tolerances were normal outside of a headache episode. In addition, as the thermal thresholds remained unaffected of the headache state, no evidence for a general hypersensitivity to pain was found. The similar decreases in EMG-levels in both groups after clenching indicate that the increased EMG-levels in patients free of headache may be a secondary characteristic. This is supported by similar findings in a recent study of patients during and outside of spontaneous tension-type headache attacks (Jensen et al. in press). Based on the present findings, results from previous studies (Jensen et al. 1993b, Jensen et al. 1994, Jensen et al. in press) and results from recent animal studies (Mense et al. 1993, Le Bars et al. 1979) on peripheral and central pain mechanisms we suggest the following mechanism of tension-type headache: involuntary contraction of muscles, due to mechanical or psychological stress, causes activation and chemical sensitization of the myofascial mechano receptors and their afferent fibres. This increased peripheral input may result in sensitization and functional reorganization of second order sensory neurons in the dorsal horn (Hoheisel et al. 1994) as stimuli in the deep myofascial tissues are much more effective in this respect than stimuli in the cutaneous tissues (Wall et al. 1984, Yu et al. 1993). Normally, increased peripheral nociceptive input is counteracted by increased activity in the antinociceptive system and no headache arises. However, in some individuals and under certain circumstances this homeostatic mechanism does not function. An abnormal sensitization arises and combined with an impaired central antinociceptive mechanism, an episode of tension-type headache may develop. However, the relative importance of peripheral and central sensitization and of the antinociceptive system remain further elucidation. In conclusion, the results obtained be the present inventors suggest that muscular factors play an important role in the initiation of a headache episode. However, the further development and transition into the chronic pain state is probably due to a central sensitization with or without impairment of the central antinociceptive system.

TABLE VIII

Clinical characteristics of the subjects studied

| | TH patients | Controls |
|---|---|---|
| Number (n) | 58 | 30 |
| Males | 22 | 12 |
| Females | 36 | 18 |
| Age(years) | 45(21-63) | 42(23-67) |
| Years with TH | 23(1-45) | - |
| Frequency of TH days/28 days | 17(8-27) | - |
| Frequency of migraine days/year (n=28) | 7(2-12) | - |

Mean values with range in brackets are given. TH indicates tension-type headache

TABLE IX

Pressure pain detection thresholds (PPDT) and tolerances (PPTO) in 58 headache patients free of headache and 30 healthy controls. Mean values of left and right side with SD in brackets are given in kPa.

| | PPDT | PPTO |
|---|---|---|
| FINGER | | |
| patients | 353(137) | 779(294) |
| controls | 358(168) | 785(289) |
| TEMPORAL REGION | | |
| patients | *220(76) | 399(146) |
| controls | 203(103) | 387(157) |
| PARIETAL REGION | | |
| patients | 323(146) | 600(190) |
| controls | 317(195) | 571(201) |

* $p < 0.05$

TABLE X

Thermal thresholds in 58 headache patients free of headache and in 30 healthy controls. Mean values of left and right side with SD in brackets are given in °C.

| | Warm detection | Pain threshold | Pain tolerance |
|---|---|---|---|
| HANDS | | | |
| patients | 34.5(1.2) | 42.3(3.0) | 47.2(2.3) |
| controls | 34.4(1.2) | 42.4(2.7) | 47.5(2.2) |
| TEMPORAL REGION | | | |
| patients | * 34.2(1.7) | 39.6(2.7) | 44.0(2.0) |
| controls | 33.8(0.8) | 39.1(2.7) | 43.9(2.9) |

* $p < 0.05$

TABLE XI

EMG levels in 58 patients free of headache and in 30 healthy controls during rest and maximal voluntary contraction(MVC). Mean values of left and right side with SD in brackets are given; RMS indicate root mean square values of amplitudes (uV) and Mean F indicate mean frequency (Hz).

| | REST | | MVC | |
|---|---|---|---|---|
| | RMS | Mean F | RMS | Mean F |
| TEMPORAL MUSCLES | | | | |
| patients | 2.7 (1.9) | 78 (22) | 164 (81) | 164 (32) |
| controls | 2.3 (0.9) | 74 (17) | 181 (101) | 155 (30) |
| TRAPEZIUS MUSCLES | | | | |
| patients | *3.5 (1.2) | 39 (9) | 246 (124) | 88 (16) |
| controls | 3.1 (0.9) | 40 (9) | 259 (131) | 88 (16) |

* $p<0.05$

**EXAMPLE 4**

A NITRIC OXIDE SYNTHASE INHIBITOR IS EFFECTIVE IN CHRONIC TENSION-TYPE HEADACHE AND IS COUNTERACTING CENTRAL SENSITIZATION

**INTRODUCTION**

Nitric oxide (NO) is an almost ubiquitous molecule that probably plays an important role in the modulation and transmission of pain (Meller and Gebhart 1993). NO is assumed to be of particular importance for the development of central sensitization, i.e. increased excitability of neurons in the central nervous system (McMahon et al. 1993; Meller and Gebhart 1993). In this way NO may contribute to the development of chronic pain. The synthesis of NO is catalysed by the enzyme NO synthase (NOS) (Moncada et al. 1991). Recent animal studies have shown that NOS inhibitors reduce central sensitization in persistent pain models (Haley et al. 1992; Hao and Xu 1996; Mao et al. 1997). Chronic tension-type headache responds poorly to analgesics and new treatments are badly needed (Rasmussen et al. 1991). The aim of the present study was to

evaluate whether intravenous infusion of the NOS inhibitor, L- $N^G$ methyl arginine hydrochloride (L-NMMA), is effective in the treatment of this disorder.

## MATERIALS AND METHODS

*Subjects*

Sixteen patients with a diagnosis of chronic tension-type headache according to the criteria of the International Headache Society (Headache Classification Committee 1988) were recruited from the out-patient headache clinic at Glostrup Hospital. There were 12 women and 4 men with a mean age (range) of 38.5 (23-52) years. Five patients with coexisting infrequent migraine (≤ one day/month) were accepted. All patients completed a diagnostic headache diary during a 4-week run-in period (Russell et al. 1992). At screening, a full physical and neurological examination, including 12-lead ECG were carried out. Blood samples for routine haematological and biochemical testing, and urine sample for urinanalysis were taken. The patients were not allowed to take analgesics 12 hours prior to the treatment. Exclusion criteria were: daily medication (including prophylactic headache therapy but not oral contraceptives); pregnant or breast feeding women; abuse of analgesics (corresponding to >2 gm of aspirin/day) or alcohol; serious somatic or psychiatric diseases including depression (Hamilton Depression Score ≥17 (Hamilton 1960)); ischemic heart disease; a supine diastolic blood pressure > 90 mmHg or heart rate < 50 beats per minute at study entry. All patients gave written informed consent to participate in the study, which was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

*Procedures*

Using a double-blind crossover design, the patients were randomised to receive 6 mg/kg L-NMMA (Clinalfa, Switzerland) or placebo (isotone glucose) on two days with a typical episode of tension-type headache separated by at least one week. Randomisation (Med.Stat) and drug preparation were performed by staff not involved in the study. The medication was given over 15 minutes into an antecubital vein (Braun Perfusor). The following parameters were measured at baseline and 15, 30, 60 and 120 minutes post administration: headache intensity on a 100-mm Visual Analog Scale (VAS) (0 - no headache and 100 - worst imaginable headache) and on a Verbal Rating Scale (VRS) from 0-10 (0 - no headache; 5 - moderate headache; 10 - worst imaginable headache). Blood pressure and pulse rate were measured 5 minutes prior to administration of treatment and at 5, 10, 15, 20, 25, 30, 60, 90 and 120 minutes post administration. Twelve-lead ECG was monitored continuously. Any adverse events were recorded. Patients with unrelieved headache at 120 minutes post treatment were allowed to take rescue medication. All patients were asked to record details of the following on a diary card at 4, 8, 12, 16, 20 and 24 hours post administration: headache intensity on VRS, any medication

taken and adverse events. Between 4-7 days after each treatment, the patients returned to the clinic, the diary cards were collected and any adverse events were noted.

*Data analysis and statistics*

Primary endpoint was the reduction of pain intensity over time on active treatment compared to placebo. The secondary endpoints were reduction of pain intensity at 30, 60, 90 and 120 minutes post dosing on VAS and VRS compared to pre-treatment pain score within each treatment. Comparison of pain intensity on VAS, blood pressure and pulse rate over time between treatments were performed with ANOVA. Paired-Samples T Test was used to compare pre-treatment pain score on VAS with pain score at 30, 60, 90, 120 minutes post dosing within each treatment. The sum of differences between the pre-treatment VRS score and the VRS score at 30, 60, 90, 120 minutes post dosing was calculated in order to obtained a summary measure of pain score for each treatment (Matthews et al. 1990). These sums of differences for each treatment were compared by Wilcoxon Signed Rank test. Five percent was accepted as level of significance.

## RESULTS

*Treatment efficacy*

L-NMMA reduced pain intensity (VAS) over time significantly more than placebo ($p=0.007$). Relative per cent changes in pain intensity from baseline are shown in Figure 15. Pain score was significantly reduced after 30, 60, 90 and 120 minutes post treatment with L-NMMA (Table 1). There was no significant reduction in pain intensity following treatment with placebo at any time points. The pain intensity on VRS was significantly lower after treatment with L-NMMA than after treatment with placebo ($p=0.02$).

*Adverse events and rescue medication*

The mean arterial blood pressure (MAP) and pulse rate changed significantly over time during treatment with L-NMMA compared with placebo ($p=0.0001$ and $p=0.0001$). The maximum increase in MAP was 12 ± 2% and occurred 15 minutes post dosing. The maximum decrease in pulse rate was 16 ± 2% and occurred 10 minutes post dosing. The increase in MAP and decrease in pulse rate are consistent with known pharmacological properties of L-NMMA. Patients were unaffected by these changes. Seven patients reported subjective symptoms in relation to the L-NMMA infusion. These were: tiredness (2), dryness of the mouth (3), drowsiness (1), exhaustion (1), nausea (1) and a feeling of tingling in arm (1). Four patients reported subjective symptoms in relation to placebo treatment. These were: a feeling of tingling in arm (2) and shoulder (2), dryness of the mouth (1), warm sensation in the body (1) and drowsiness (1). No patients withdrew from the study because of side effects. Three patients

treated with L-NMMA and 7 patients treated with placebo used simple analgesics as rescue medication.

## DISCUSSION

There is ample experimental evidence showing that persistent activity in peripheral nociceptors may lead to sensitization of spinal dorsal horn neurons partly via activation of N-methyl-D-aspartate (NMDA) receptors (Coderre et al. 1993). Since many of the effects of the NMDA receptor activation are mediated through production of NO, it seems probable that NO plays an important role in the hyperalgesia in the spinal cord (Meller and Gebhart 1993). In support for this, animal models have shown that NOS inhibitors reduce spinal dorsal horn sensitization induced by continuos painful input from the periphery (Haley et al. 1992; Hao and Xu 1996; Roche et al. 1996). However, the efficacy NOS inhibitors have not previously been examined in patients.

Recently, it has been demonstrated that spinal dorsal horn sensitization due to prolonged nociceptive input from pericranial myofascial tissues probably plays an important role in the pathophysiology of chronic tension-type headache (Bendtsen et al. 1996a, 1996b; Jensen et al. 1997). Thus, it is likely that the analgesic effect of L-NMMA in chronic tension-type headache is due to reduction of central sensitization at the level of the spinal dorsal horn.

In conclusion, the present study provides the first evidence of an effect of NOS inhibitors in human chronic pain, and indicates that the effect of NO is via reduction of central sensitization probably at the level of the dorsal horn/trigeminal nucleus.

Table XII

Pain scores on VAS before treatment and at 30, 60, 90 and 120 minutes post dosing. Mean values (SD) are given.

| | Baseline | 30 minutes | 60 minutes | 90 minutes | 120 minutes |
|---|---|---|---|---|---|
| L-NMMA | 49 ± 16 | 38 ± 18* | 35 ± 18* | 34 ± 21* | 33 ± 21* |
| Placebo | 44 ± 14 | 41 ± 17 NS | 40 ± 17 NS | 42 ± 16 NS | 40 ± 17 NS |

* = $p < 0.05$ and NS = not significant compared with pretreatment values (Paired-Samples T Test).

**EXAMPLE 5**

MUSCULAR FACTORES ARE OF IMPORTANCE IN TENSION-TYPE HEADACHE

**Introduction**

A recent study from by the present inventors demonstrated for the first time that chronic tension-type headache has a physiological basis and is caused at least partly by qualitative changes in the central processing of sensory information (Bendtsen et al. 1996b). It was suggested that muscular disorders are of primary importance for the development of central sensitisation. To test this hypothesis, the present study of the psychophysical tests suggested in the IHS classification (Headache Classification 1988) as well as thermal pain sensitivity was conducted. The primary aim was to compare the mechanical and the thermal pain sensitivity in tension-type headache patients with and without disorders of pericranial muscles. The secondary aim was to study the clinical characteristics of these patients.

**Patients and Methods**

*Patients*

Fifty-eight patients with tension-type headache fulfilling the IHS-criteria (Headache Classification 1988) were included (Table XIII). Twenty-nine patients had frequent episodic tension-type headache (ETH) and 29 patients had chronic tension-type headache (CTH). The patients were recruited from the out-patient headache clinic at Gentofte Hospital and complete physical and neurological examinations were done before entry. According to the primary aim patients with restricted tenderness in the pericranial muscles were favoured, since the percentage of patients associated with muscular disorders is 80-90% in consecutive populations

(Jensen et al., 1996, Langemark et al., 1988). Further inclusion criteria were duration of tension-type headache for at least one year and age between 18 and 70 years. The exclusion criteria were: migraine more than 1 day per month, cluster headache, trigeminal neuralgia, other neurological, systemic or psychiatric disorders, ingestion of major medications including prophylactics for migraine or other headaches, any form of drug abuse or dependency as daily ergotamine or large amounts of plain analgesics.

Thirty healthy subjects (12 males and 18 females) with a mean age of 42 years (range 23-67 years) and without tension-type headache (< 14 days tension-type headache/year) were used as controls. Informed consent was obtained and the study was approved by the local ethical committee. The present study was a part of a multifaceted study of tension-type headache, of which other parts have been published previously (Jensen, 1996, Jensen and Olesen, 1996).

**Procedure**

All patients had to fill in a diagnostic headache diary during a 4 week run-in period to ensure that they fulfilled the inclusion criteria. Patients were instructed to fulfil the diary at the end of each day with headache and to record the mean intensity on a 0-3 scale, where 0 was no pain and 3 was severe incapacitating pain that requires bed rest (Russel et al., 1992). The approximate start and disappearance of headache and the total intake of analgesics or other medications should also be recorded. A standard dose of analgesics was defined as a dose equivalent to 1000 mg of aspirin. All patients were examined when free of headache and were not allowed to have taken any analgesics on the day of examination.

**Examination**

The examination was performed in a standardized way, which has been described previously (Jensen, 1996, Jensen and Olesen, 1996). All recordings were performed by the same observer, the technician, throughout the entire study and the observer was blinded for the following subdivision of patients. Before recordings of pain thresholds each individual was carefully instructed to apply the same interpretation of 'painful' throughout the study. Initial test sessions were applied to all subjects in order to familiarize them with the test conditions.

**Palpation**

Pericranial tenderness was evaluated by palpation of 9 pairs of pericranial muscles and tendon insertions by the technician in a standardized, randomized procedure (Langemark and Olesen, 1989, Jensen et al., 1993b, Bendtsen et al., 1995a). Tenderness was scored in each location according to an ordinal scale from 0 to 3, and scores from all sites were summated. The

maximum possible score was thus 54 points. This Total Tenderness Score system(TTS) (Langemark and Olesen, 1987) has previously proved to be reliable (Bendtsen et al., 1995). We have previously demonstrated that the most ideal cut-off point for separating tension-type headache subjects from non-headache subjects with respect to muscle tenderness was the 75% quartile of TTS obtained from a general population, whereas pressure algometry and EMG provided no further information (Jensen et al., 1996). In the following, TTS is used as the only criteria for further subdivision patients with TTS above 9 (equal to the 75% quartile of TTS from healthy controls) was classified as having an association with muscular disorder (MUS), whereas those with TTS value at 9 or below were classified as unassociated with such a disorder (non-MUS).

**Pressure Pain Thresholds**

The pressure pain thresholds were evaluated bilaterally on the distal dorsal part of the second finger, and in two cranial locations, one with interposed temporal muscle (Temp) and one without interposed muscle in the parietal region (Par). A standardized and previously evaluated method was applied using an electronic pressure algometer (Somedic AB, Sweden) with an 0.79 $cm^2$ circular stimulation probe (Petersen et al., 1992, Jensen et al., 1986, Brennum et al., 1989). Two pain qualities were recorded, the Pressure Pain Detection Threshold (PPDT) defined as the threshold, where the pressure sensation became painful, and the Pressure Pain Tolerance (PPTO) defined as the threshold where the patient would no longer tolerate the pain (Petersen et al., 1992). By pressing a hand held button the subjects indicated that the threshold was reached, and the pressure was released immediately. If patients did not activate the button, the experiment was terminated when reaching 800 kPa in the cranial region and 1500 kPa in the fingers. Each threshold was calculated as the median value of 3 determinations performed with intervals of 10-15 seconds, and mean values of left and right sided recordings are presented in the following.

**Thermal Pain Thresholds**

Thermal thresholds were evaluated with a computerized version of the Thermotest (Somedic AB, Sweden) (Fruhstorfer et al., 1976, Yanrnitsky et al., 1995). The thermode consisted of series-coupled Peltier elements and measured 25x50 mm. The thenar region of the hand and the anterior part of the temporal region were examined bilaterally. Three stimulation qualities were recorded; the Warm Detection limit (WD) defined as the lowest temperature detected as warm, the Heat Pain Detection (HPD) defined as the temperature where the heat sensation became painful, and the Heat Pain Tolerance (HPTO) defined as the highest temperature tolerated (Jensen et al., 1996, Jensen and Olesen, 1996). A baseline temperature of 32 °C and a 1.0 °C/sec

rate of temperature change was used. Heat stimulation was terminated when reaching 52 °C, if the patients had not responded before. By pressing a hand-held button the subjects indicated when the actual threshold was reached. This value was recorded automatically and the stimulator returned to baseline. Each threshold was calculated as the average of 5 determinations performed with intervals of 10-15 seconds, and mean values of left and right sided recordings are presented in the following.

### Electromyography

EMG signals from the temporal and trapezius muscles were recorded bilaterally by a 4-channels electromyograph (Counterpoint, Dantec, Copenhagen). A standardized, previously described method was applied (Jensen et al., 1993). Data were collected during rest in the supine position and during maximal voluntary contractions (MVC) (jensen et al., 1996). The root mean square (RMS) voltage was measured. Power spectrum was calculated for the frequency range 0 to 1 kHz and Mean Frequencies (Mean F) were extracted (Jensen et al., 1996).

## STATISTICS

Clinical data are presented as mean values with range (Table XIII and XIV) and the psychophysical data as mean values ±SE. Mann-Whitney's U test was used for testing unpaired observations in patients with and without association with muscular disorders. Analysis of variance was used to control for the variations in sex distribution among the groups. Spearman's test was used for calculation of coefficients of correlation. Five percent was accepted as level of significance.

## RESULTS

Two patients (a male with the episodic and a male with the chronic subform) were excluded from the present study due to deficient diaries. The remaining 56 patients, 28 with CTH and 28 with ETH completed the study and detailed clinical data with respect to their association with muscular disorder are presented in Table XIII and Table XIV. Fourteen patients with chronic tension-type headache had a history of coexisting migraine with a mean value of 7.3 days with migraine per year, not significantly different from the 15 ETH patients, who had a history of 7.7 days with migraine per year. Similarly, there was no significant difference between the prevalence of migraine in patients with muscular disorders compared to those without such disorder. No significant variations in the clinical characteristics between patients with and without disorders of pericranial muscles could be detected (Table XIII,XIV).

**Tenderness recorded by manual palpation.**

According to the prior definition of association with muscular disorders, CTH patients associated with muscular disorder (MUS) had, as expected, significantly higher TTS at 18.5 compared to 6.2 in those without such an association (non-MUS) ($p<0.0001$). Similarly, ETH patients with MUS had significantly higher TTS at 15.3 compared to 4.3 in those without such an association ($p<0.0001$).

**Pressure Pain thresholds**

Pressure pain detection and tolerance thresholds were significantly lower in CTH patients associated with MUS compared to non-MUS patients in all the examined locations (PPDT $p<0.001$ ; PPTO $p<0.05$) (Table XV) (Fig 16).
In patients with ETH, there were no significant differences in the pressure pain thresholds and tolerances between subjects with or without association with muscular disorders in any of the examined locations (Table XVI) (Fig 17).

**Thermal pain thresholds**

There were no significant differences in heat detection, heat pain and heat pain tolerance thresholds from the hands and the temporal regions between CTH patients with and without a muscular disorder. Similarly, no significant variations in thermal thresholds could be detected in ETH patients with and without a muscular disorder.

**Relation between tenderness and pain thresholds**

In CTH patients, the Total Tenderness Score (TTS) was highly correlated to the mechanical pain thresholds at the temporal region (Temp: TTS vs PPDT:$r= -0.61$, $p<0.001$; TTS vs PPTO:$r= -0.65$, $p<0.001$), and a similar tendency was seen at the parietal region (TTS vs PPDT $r=-0.59$, $p=0.003$; TTS vs PPTO $r=-0.24$, $p=0.27$) and at the extracephalic region (Hands: TTS vs PPDT $r=-0.36$, $p=0.06$, TTS vs PPTO, $r=-0.48$, $p=0.02$). No such relations could be detected in ETH patients in any of the examined locations. When TTS was correlated to thermal thresholds no significant relations appeared either in the chronic or the episodic form.

**EMG**

When EMG levels were recorded from the temporal and the trapezius muscles under resting conditions and during maximal voluntary contraction, CTH patients with association to

muscular factors had significantly higher RMS values in their trapezius muscles during resting condition compared to non-MUS patients ($p=0.02$). No other significant differences between the 2 subgroups in neither CTH nor ETH patients appeared.

**Relation to healthy controls**

*Tenderness by manual palpation*

The mean Total Tenderness Score(TTS) in the 30 healthy controls was 4.7 (quartiles 0-9) and was significantly lower than 9.8 (quartiles 4-15) in those 28 patients with ETH ($p=0.002$). In CTH patients TTS was 14.1 (quartiles 4-15) and significantly higher than in ETH patients ($p=0.03$) and in healthy controls ($p<0.0001$).

*Pressure Pain Thresholds*

Compared to healthy controls, CTH patients with non-MUS had significantly higher pressure pain thresholds and tolerance thresholds in all the examined locations ($p<0.01$), whereas the mechanical tolerances tended to be significant lower in CTH patients with MUS (Fingers PPTO, $p=0.07$; Temp PPTO $p=0.05$). No significant differences could be detected in the parietal regions or in pressure pain detection thresholds from the other locations. When pressure pain detection and tolerance thresholds from the 2 subgroups of ETH patients were compared to those from healthy controls no significant differences appeared.

*Thermal Pain Thresholds*

When the thermal thresholds were compared to healthy controls, significantly higher values of all the tested qualities were noted in cephalic locations in those 10 CTH patients without association with muscular disorders, whereas only warm detection values were higher on the hands of these patients (Temporal:WD $p=0.02$,WPDT $p=0.04$,WPTO $p=0.028$; Hands:WD $p=0.02$). No significant variations in thermal thresholds could otherwise be detected in relation to healthy controls.

*EMG*

Only CTH patients associated with muscular factors had significantly higher RMS values in the temporal($p=0.008$) and the trapezius muscles during rest ($p=0.004$) than healthy controls. No other differences between patients and controls were noted.

## DISCUSSION

*Relation between tenderness and pain thresholds*

In the present study highly significant inverse correlations between TTS, pressure pain detection and tolerance thresholds were found in patients with CTH corresponding with our recent study (Bendtsen et al., 1996). Others have reported relatively small and clinically insignificant relations (Schoenen et al, 1991a, Jensen et al., 1996, Sandrini et al., 1994), and the pressure pain thresholds provided only limited diagnostic value (Jensen et al., 1996). This discrepancy may be due to the fact that the pressure pain threshold represents the lower end, and the pressure pain tolerance the upper end of a pain stimulus response curve. Tenderness obtained by manual palpation elicit pain intensities between these extremes where the difference between patients and controls is largest as discussed recently by Bendtsen et al (Bendtsen et al., 1996b, Bendtsen et al., 1996c). The diagnostic tests given in the IHS classification were previously assessed in a study from a highly specialized headache clinic (Snadrini et al., 1994) and in subjects from a general population (Jensen et al., 1996). In the latter study, 87% of subjects with chronic, and 66 % of subjects with episodic tension-type headache had a disorder of the pericranial muscles (Jensen et al., 1996). In the former, Sandrini et al reported that 61% of patients with episodic, and 66% of patients with chronic tension-type headache had disorder of pericranial muscles. An earlier study, where only EMG and pressure algometry were assessed, 72% were found to be associated with disorders of pericranial muscles (Schoenen et al., 1991). Tenderness determined by manual palpation was previously found to be the most sensitive and specific test for disorder of pericranial muscles (Jensen et al., 1996) and was therefore applied as the only test to separate the 2 subforms in the present study.

*Pathophysiological mechanisms of the disorders of pericranial muscles*

It has been uncertain whether the increased, pericranial myofascial tenderness was the cause or the effect of the pain. A recent, experimental study indicated, however, that tenderness precedes the induced headache by several hours when tension-type headache is induced by tooth clenching (Jensen et al., 1996). Possible mechanisms for the tenderness include 1) sensitization of peripheral myofascial nociceptors; 2) sensitization of second order neurons at the spinal/trigeminal level; 3) impaired central modulation of the nociceptive activity. As tension-type headache is a disease in man and not known in animals, experimental animal models are of limited value for evaluation of these mechanisms. Fortunately, quantitative analyses of mechanical and thermal pain thresholds in humans can be used for this purpose. Thermal pain- and tolerance thresholds are normal in most of these patients, which indicates that pain mediated by C-fibers is registered and modulated normally. The present finding of markedly increased tenderness, slightly decreased mechanical but normal thermal thresholds at cephalic and extracephalic locations in CTH patients associated with muscular disorder, strongly

indicates a hyperalgesic response to mechanical stimulation in these patients in line with previous studies (Bendtsen et al., 1196c, Schoenen et al., 1991b, Lnagemark et al., 1989). This is also supported by our findings of a highly significant inverse relation between tenderness and mechanical threshold. It has recently been demonstrated that due to central sensitization, pain in CTH and in fibromyalgia may be mediated via low-threshold mechanosensitive afferents projecting to dorsal horn neurons (Bendtsen et al., 1996c, Bendtsen et al. in press). This is supported by prior observations by Bendtsen et al., where an abnormal qualitative stimulus response function was found only in those 20 CTH patients with the most pronounced tenderness whereas 20 patients without abnormal tenderness exhibited a fairly normal stimulus response curve (Bendtsen et al., 1996c). A further support for myofascial involvement is the finding of increased EMG amplitude levels only from the pericranial muscles of CTH patients associated with muscular disorders, whereas EMG levels otherwise were similar to those in controls. The mechanisms of pain in tension-type headache without association with a muscular disorder cannot be explained by simple allodynia and/or hyperalgesia as both mechanical and thermal pain thresholds from these patients were significantly increased compared to healthy controls, indicating a higher pain tolerability. Therefore, other mechanisms, probably in the central modulation of pain, must be considered. As the clinical features examined in the present study were fairly similar between the 2 subgroups in both the episodic and the chronic form it is very likely, however, that several pathophysiological mechanisms are shared and further documentation about the fairly rare patients with tension-type headache without association with muscular disorders are highly needed. Taken together our data strongly suggest that central sensitization is of key importance in chronic tension-type headache with disorders of pericranial muscles, whereas other mechanisms must be considered in patients without such disorders.

*Relationship between episodic and chronic tension-type headache*

The present study is the first study which have examined this wide variety of clinical characteristics and psychophysical tests in both episodic and chronic tension-type headache. A marked difference in nociceptive mechanical thresholds between the 2 subgroups in the chronic, but not in the episodic form was demonstrated, whereas tenderness recorded by manual palpation was highly increased in both the episodic and the chronic tension-type headache. A hypothesis of the pathophysiological evolution of tension-type headache can therefore be created. In ETH patients with disorder of pericranial muscles, the most likely mechanism is a slightly increased input from myofascial nociceptors projecting to a widely normal central pain perception system. As chronic tension-type usually evolves from the episodic form (Langemark et al., 1989) it is suggested that prolonged painful input from the periphery may sensitize the central nervous system and that the pain in CTH associated with muscular disorder thus may be due to a central misinterpretation of the incoming signals at the dorsal horn or trigeminal

level. Such mechanisms have been demonstrated in animal models (Coderre et al., 1993, mense et al., 1993, Hu et al., 1992, Hoheisel et al., 1994), and irritative stimuli from myofascial, deep tissues are found to be much more effective for induction of central sensitisation than cutaneous stimuli (Yu et al., 1993). Muscular disorders may therefore be of major importance for the conversion of episodic into chronic tension-type headache. As the most frequently reported precipitating factors leading to tension-type headache are stress, mental tension and tiredness (Rasmussen et al., 1993, Clark et al., 1995, Ulrich et al., 1996), central supraspinal involvement is undoubtedly also involved, although precipitating factors may be different from causative factors. Whether the precipitating factors and the evolution of pain vary between the patients with and with disorders of pericranial muscles remains to be elucidated.

In conclusion, the present data indicate that the fine balance between peripheral nociceptive input and their central modulation seems to be disturbed in the majority of patients with tension-type headache, namely those associated with muscular disorders. An a central misinterpretation of the incoming peripheral stimuli may be the result, a vicious circle is started and is probably maintained long time after the primary eliciting stimuli/stressor had stopped. Disorders of pericranial muscles may therefore be of major importance for the conversion of episodic into chronic tension-type headache, whereas other mechanisms should be considered for those patients without such disorders. The present study supplements the understanding of the interaction between peripheral and central changes in tension-type headache, and thereby, hopefully, will lead to a better understanding, prevention and treatment of the most prevalent type of headache.

TABLE XIII

Clinical characteristics of patients with chronic tension-type headache (N=28)

| | Patients with MUS | Patients without MUS |
|---|---|---|
| Number (n) | 18 | 10 |
| Males/females | 7/11 | 7/3 |
| Age(years) | 48.1 (34-64) | 49.4 (37-59) |
| Years with TH | 24.8 (1-45) | 26.2 (2-50) |
| Frequency of TH (days/28 days) | 22.6 (15-28) | 23.7 (15-28) |
| Intensity (0-3 scale) | 1.7 (1-2.5) | 1.4 (1-2) |
| Duration (hours) | 11.3 (4.2-24) | 9.5 (2.9-24) |
| Medication (doses/day) | 1.6 (0-3.1) | 1.8 (0-4.1) |

Mean values with range in brackets are given. MUS indicate association with muscular disorder as defined in the text, and without MUS indicate no such association. TH indicates tension-type headache.

TABLE XIV

Clinical characteristics of patients with episodic tension-type headache(N=28)

| | Patients with MUS | Patients without MUS |
|---|---|---|
| Number (n) | 14 | 14 |
| Males/females | 1/13 | 5/9 |
| Age(years) | 39.8 (20-56) | 42.6 (21-59) |
| Years with TH | 20.2 (2-40) | 19.6 (8-30) |
| Frequency (days/28 days) | 9.6 (5-14) | 10.0 (6-14) |
| Intensity (0-3 scale) | 1.7 (1.0-2.1) | 1.8 (1.4-2.2) |
| Duration (hours) | 9.7 (4.7-18) | 8.6 (3.3-24) |
| Medication (doses/day) | 1.0 (0-2) | 0.8 (0-1.4) |

Mean values with range in brackets are given. MUS indicate association with muscular disorder as defined in the text, and without MUS indicate no such association. TH indicates tension-type headache.

TABLE XV

Pressure pain detection and tolerance thresholds in patients with chronic tension-type headache (N=28). Mean values are given in kPa with SE in brackets.

| | Patients with MUS (n=18) | Patients without MUS (n=10) | p-value |
|---|---|---|---|
| *Pain detection thresholds* | | | |
| Fingers | 262 (17) | 374 (23) | $p<0.001$ |
| Temporal region | 143 (9) | 241 (18) | $p<0.0001$ |
| Parietal region | 217 (18) | 368 (28) | $p<0.001$ |
| *Pain tolerance thresholds* | | | |
| Fingers | 535 (32) | 776 (50) | $p<0.001$ |
| Temporal region | 252 (17) | 394 (23) | $p<0.0001$ |
| Parietal region | 471 (38) | 521 (27) | $p=0.04$ |

TABLE XVI

Pressure pain detection and tolerance thresholds in patients with episodic tension-type headache (N=28). Mean values are given in kPa with SE in brackets.

| | Patients with MUS (n=14) | Patients without MUS (n=14) | p-value |
|---|---|---|---|
| *Pain detection thresholds* | | | |
| Fingers | 247 (12) | 269 (18) | p=0.14 |
| Temporal region | 162 (10) | 169 (10) | p=0.72 |
| Parietal region | 223 (16) | 221 (16) | p=0.89 |
| *Pain tolerance thresholds* | | | |
| Fingers | 610 (34) | 595 (50) | p=0.47 |
| Temporal region | 317 (18) | 327 (23) | p=0.98 |
| Parietal region | 453 (23) | 449 (30) | p=0.85 |

## EXAMPLE 6

## GABAPENTIN HAS A PROPHYLACTIC EFFECT IN CHRONIC TENSION-TYPE HEADACHE

### INTRODUCTION

GABA is an important inhibitory transmitter in the central nervous system and it has been suggested that the encoding of low-threshold mechanical threshold stimuli depends upon the presence of a tonic activation of intrinsic glycine and/or GABAergic neurons (Yaksh and Malmberg 1994). Gabapentin was synthesized to be a systemically active GABA analogue and was found to have anticonvulsant effect. Although initially employed in humans to control seizures, recent clinical cases indicated that the agent showed efficacy in treating human neuropathic pain states (Rosner et al 1996), and a considerably effect in several experimental pain models (Hwang and Yaksh 1996, Xiao and Bennett 1996). The exact mechanism is not fully understood, but several mechanisms have been suggested. Binding studies fail to show affinity for either GABA A or GABA B, although Gabapentin can increase the rate of GABA synthesis and release. Furthermore, Gabapentin showed binding affinity to the alpha-2-subunit of a calcium channel (Gee et al. 1996), and these calcium channels are recently reported to play a very exciting role in the genetic studies of migraine disorders. As the side effect profile of Gabapentin is favourable, the prophylactic effect of Gabapentin in a small open labelled pilot study in patients with chronic tension-type headache was evaluated.

### MATERIALS AND METHODS

Three patients with a diagnosis of chronic tension-type headache according to the International Headache Society (Headache Classification Committee 1988) were recruited from the outpatient headache clinic at Glostrup Hospital. The patients were males with a mean age of 42 years (range 35-49). The mean life time duration of chronic tension-type headache was 16 years (range 7-21). Two patients had a coexisting but infrequent migraine. Exclusion criteria were: daily major medication (including prophylactic headache therapy); abuse of analgesics or alcohol; serious somatic or psychiatric diseases including depression.

#### Procedures

Using an open labelled design, patients fulfilled a diagnostic headache diary during at least 4 weeks run-in period to ensure the diagnostic criteria. Thereafter, the patients received Gabapentin (Neurontin®) tablets, initially 300 mg (one tablet) per day on day one, increasing

with 300 mg (1 tablet) per day to 900 mg (3 tablets) on day 3. The treatment period lasted 4 weeks, and during this period patients were asked to continue with headache diaries, and record headache intensity, frequency, duration, any medication taken and any possible adverse events. At a follow up visit at day 29-32, diaries were collected and any adverse events and evaluation of the treatment were recorded.

Due to the low number of patients, no statistical analysis were done. The primary efficacy parameters were headache intensity, frequency and duration, and the mean values from the run-in period were compared to those obtained during the treatment period.

## RESULTS

All patients completed the study. Headache intensity decreased 35%, namely from 5.5 on a 0-10 VAS intensity scale during run-in period to 3.6 during active treatment. Duration of the individual headache episode was reduced by 8%, and frequency of headache decreased by 45%, namely from 23.5 days per 4 weeks during run-in period to 13 days per 4 weeks during the active treatment period. The mean daily intake of analgesics decreased by 72% from 1.1 dose per day to 0.3 dose per day. One patient had excellent effect of Gabapentin with complete relief of the headache after 2 days treatment, another patient had a moderate effect on headache intensity and frequency, and the third patient had no significant effect on any of efficacy parameters. Those two subjects with good or excellent effect reported no side effects, whereas the third patient who had no beneficial effect of Gabapentin complained of sedation, vertigo and slight nausea. These side effects disappeared completely after cessation of the drug intake.

## DISCUSSION AND CONCLUSION

The present results suggest a positive prophylactic effect of Gabapentin in chronic tension-type headache, which is in accordance with the predictions made from the model involving central sensitization provided by the present invention. Although the exact mechanism of action of gabapentin is not fully elucidated, the preliminary experimental evidence are highly in favour of a pathophysiological explanation of chronic tension-type headache, as caused by central sensitization.

EXAMPLE 7

DEXTROMETHORPHAN HAS A PROPHYLACTIC EFFECT IN CHRONIC TENSION-TYPE HEADACHE

INTRODUCTION

The common role played by NMDA antagonism in preclinical models is consistent with the observation that systemic ketamine reduces the allodynia, hyperalgesia and after sensation present in patients with peripheral pain injury, and the magnitude of the relief is, in general, proportional to dose. Dextromethorphan has been shown to reduce the after sensation induced by repetitive stimuli in human volunteers (Price et al 1994). Furthermore, the NMDA receptors are shown to act on the neuronal excitability via opening or closing of ion channels. The increase in intracellular calcium by such opening of the ion channels is believed to initiate a cascade of biochemical events, including pain. Effective blockade of these events is possible by NMDA antagonists, which are also highly effective in various human pain conditions related to central sensitization (Persson et al 1995). The major problem in this treatment strategy is, however, the central side effects of most NMDA antagonists. Dextromethorphan has been known for decades as a cough suppressant and has a very favourable side effect profile. Therefore the prophylactic effect of Dextromethorphan was evaluated in a small, open labelled pilot study in patients with chronic tension-type headache.

MATERIALS AND METHODS

Five patients with a diagnosis of chronic tension-type headache according to the International Headache Society (Headache Classification Committee 1988) were recruited from the outpatient headache clinic at Glostrup Hospital. There were 2 males and 3 females, and the mean age was 45.4 years (range 39-48). The mean life time duration of chronic tension-type headache was 12.2 years (range 4-25). One patient had coexisting but infrequent migraine. Exclusion criteria were: daily major medication (including prophylactic headache therapy); abuse of analgesics or alcohol; serious somatic or psychiatric diseases including depression.

**Procedures**

Using an open labelled design, patients fulfilled a diagnostic headache diary during at least 4 weeks run-in period to ensure the diagnostic criteria. Thereafter, the patients received Dextromethorphan (Dexofan®) tablets at 30 mg each, three times per day. The treatment period lasted 4 weeks, and during this period patients were asked to continue with headache diaries,

and record headache intensity, frequency, duration, any medication taken and any possible adverse events. At a follow up visit at day 29-32, diaries were collected and possible adverse events and evaluation of the treatment were recorded. Due to the restricted number of patients, no statistical analysis were done. The efficacy parameters were headache intensity, frequency and duration, and intake of simple analgesics. Mean values from the run-in period were compared to those obtained during the treatment period.

## RESULTS

All patients completed the study. The intensity of headache was reduced 18% namely from 4.4 on a 0-10 VAS intensity scale during the run-in period to 3.6 during active treatment. Duration of the individual headache episode was reduced by 11%, and frequency of headache decreased by 4%, namely from 28 days per 4 weeks period during run-in to 27 days per 4 weeks period during active treatment. Intake of analgesics decreased by 72% from a mean intake at 1.8 dose per day during run-in period to 0.5 dose per day during active treatment. Two patients reported a marked effect with considerable relief of headache intensity and duration within very few days of treatment, one patient had a slight relief of headache intensity and two patients reported no effect at all. Four patients reported no side effects, and marked side effects with sedation was reported in one patient, the patient with best clinical response. These side effects diminished considerably after a dose reduction to 40 mg per day.

## DISCUSSION AND CONCLUSION

The present results suggest a positive prophylactic effect of Dextromethorphan in chronic tension-type headache. The lack of effect in some patients may be due to a relatively small dosage. Although the exact mechanism of Dextromethorphane is not fully elucidated, the preliminary evidence in experimental pain model is in favour of an effect according to the present, pathophysiological model of chronic tension-type headache, i.e. the central sensitization model of the present invention.

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## Claims

1. A method for treatment of tension-type headache in a person in need of such treatment, comprising interacting with neuronal transmission connected with pain perception, so as to obtain a substantial normalization of an otherwise qualitatively altered stimulus/response function in connection with nociception, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

2. A method for treatment of tension-type headache in a person in need of such treatment, comprising interacting with neuronal transmission connected with pain perception so as to obtain a substantial normalization of an otherwise abnormally low pain threshold in connection with chronic contraction of muscle, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

3. A method according to claim 1, wherein the interaction comprises interacting with neuronal transmission connected with second order nociceptive neurons, so as to obtain a substantial normalization of an otherwise qualitatively altered stimulus/response function in connection with nociception, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

4. A method according to claim 1, wherein the interaction comprises a reduction of input to second order nociceptive neurons, so as to obtain a substantial normalization of an otherwise qualitatively altered stimulus/response function in connection with nociception, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

5. A method according to any of the preceding claims, wherein the interaction is effected by administering an effective amount of a substance interacting with neuronal transmission connected with pain perception, the administration being performed substantially at least once daily and being continued for a period of at least one month, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

6. A method according to claim 1, wherein the interaction is one which in a panel of test persons suffering from increased myofascial tenderness with disorder of pericranial muscle in connection

with tension-type headache will transform a substantially linear pain intensity perception in response to pressure intensity in trapezius muscle into a curve (C) of which the values of pain intensity are lower than the linear pain intensity perception, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

7. A method according to claim 5, wherein the effective amount of the substance is an amount which in a panel of test persons suffering from increased myofascial tenderness in connection with tension-type headache will transform a substantially linear pain intensity perception in response to pressure intensity in trapezius muscle into a curve (C) of which the values of pain intensity are lower than the linear pain intensity perception, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

8. A method according to claim 6 or 7, wherein the curve (C) can be described substantially as a power function and is a curve which is substantially linear in a double logarithmic plot, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

9. A method for treatment or prophylaxis of tension-type headache in a person in need of such treatment, comprising interacting with neuronal transmission connected with pain perception, so as to obtain a substantial prevention of a qualitatively altered stimulus/response function in connection with nociception, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

10. A method according to claim 9, wherein the interaction is effected by administering an effective amount of a substance interacting with neuronal transmission connected with pain perception, the administration being performed substantially at least once daily and being continued for a period of at least one month, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

11. A method according to claim 9 or 10, wherein the prevention of a qualitatively altered stimulus/response function in connection with nociception leads to a reduction in pain associated with the tension-type headache, with the proviso that said interaction is not

performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

12. A method according to claim 6-8, wherein substantially each of the values of curve (C) is at the most 20% higher than the value of the corresponding curve produced for a test panel of healthy controls, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

13. A method according to claim 6-8, wherein substantially each of the values of curve (C) is at the most 10% higher than the value of the corresponding curve produced for a test panel of healthy controls, with the proviso that said interaction is not performed by Flupirtin or a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

14. A method for treatment or prophylaxis of tension-type headache in a person in need of such treatment, comprising
administering an effective amount of a substance which is a substance capable of decreasing or substantially preventing pain in connection with tension-type headache, and which, in the peripheral and/or central nervous system, is capable of specifically interacting with neuronal transmission connected with pain perception and which, in the peripheral and/or central nervous system, is further capable of

substantially blocking the production of glutamate or
substantially blocking the release of glutamate or
substantially counteracting the action of glutamate or
substantially blocking receptors for glutamate or
substantially blocking the production of 5-HT or
substantially blocking the release of 5-HT or
substantially counteracting the action of 5-HT or
substantially blocking 5-$HT_{2,3}$ receptors or
substantially enhancing the production of GABA or
substantially enhancing the release of GABA or
substantially enhancing the action of GABA or
substantially activating receptors for GABA or
substantially blocking the production of substance P or
substantially blocking the release of substance P or
substantially counteracting the action of substance P or
substantially blocking the receptors for substance P or

substantially blocking the production of nitric oxide or
substantially counteracting the action of nitric oxide or
substantially blocking the production of nitric oxide synthase (NOS) or
substantially counteracting the action of nitric oxide synthase (NOS) or
substantially blocking the production of guanylate cyclase or
substantially counteracting the action of guanylate cyclase or
substantially blocking the production of cyclic guanylate monophosphate (cGMP) or
substantially counteracting the action of cyclic guanylate monophosphate (cGMP) or
substantially blocking any further steps in the reaction induced by cyclic guanylate monophosphate (cGMP) or
substantially blocking the production of CGRP or
substantially blocking the release of CGRP or
substantially counteracting the action of CGRP or
substantially blocking receptors for CGRP or
substantially blocking the production of neurokinin A or
substantially blocking the release of neurokinin A or
substantially blocking the production of neurokinin B or
substantially blocking the release of neurokinin B or
substantially blocking the production of bradykinin or
substantially blocking the release of bradykinin or
substantially counteracting the action of bradykinin or
substantially blocking the receptors for bradykinin or
substantially blocking the production of PACAB or
substantially blocking the release of PACAB or
substantially counteracting the action of PACAB or
substantially blocking receptors for PACAB or
substantially blocking the production of adenosine or
substantially blocking the release of adenosine or
substantially counteracting the action of adenosine or
substantially blocking adenosine A2 receptors or
substantially enhancing the production of adenosine or
substantially enhancing the release of adenosine or
substantially enhancing the action of adenosine or
substantially activating adenosine A1 receptors or
substantially enhancing the production of galanine or
substantially enhancing the release of galanine or
substantially enhancing the action of galanine or
substantially activating receptors for galanine or

substantially enhancing the production of norepinephrine or
substantially enhancing the release of norepinephrine or
substantially enhancing the action of norepinephrine or
substantially activating receptors for norepinephrine or
substantially blocking the production of glycine or
substantially blocking the release of glycine or
substantially counteracting the action of glycine or
substantially blocking receptors for glycine or
substantially blocking the production of histamin or
substantially blocking the release of histamin or
substantially counteracting the action of histamin or
substantially blocking the receptors for histamin or
substantially blocking the production of neurotrophins or
substantially blocking the release of neurotrophins or
substantially counteracting the action of neurotrophins or
substantially blocking receptors for neurotrophins or
substantially blocking $Na^+$ ion channels or
substantially blocking $Ca^{2+}$ ion channels,

with the proviso that said substance is not Flupirtine.

15. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of glutamate or substantially blocking the release of glutamate or substantially counteracting the action of glutamate or substantially blocking receptors for glutamate, with the proviso that the substance is not Flupirtine.

16. A method according to claim 15 or 14, wherein the substance is a glutamate receptor antagonist.

17. A method according to claim 16, wherein the substance is an NMDA glutamate receptor antagonist.

18. A method according to claim 17, wherein the substance is a competitive NMDA glutamate receptor antagonist.

19. A method according to claim 18, wherein the substance is a diacidic piperidine, such as CGS 19755 (1) or a diacidic piperazine, such as (*R*)-CPP (2) or a diacidic piperazine, such as (*R*)-

CPPene (3) or a phosphono amino acid such as LY 235959 (3a) or derivatives of any of the above which are competitive NMDA antagonists or prodrugs thereof.

20. A method according to claim 17, wherein the substance is a non-competitive NMDA glutamate receptor antagonist.

21. A method according to claim 20, wherein the substance is a polycyclic amine, such as MK-801 (4) or a tricyclic antidepressivum, such as Metapramine (4a) or Amitriptyline (4b) or Imipramine (4c) or Desipramine (4d), or Mirtazapine (4d) or Venlafaxine (4e) or an adamantanamine, such as Memantine (5) or an arylcyclohexylamine, such as Ketamine (6) or an arylcyclohexylamine, such as Norketamine (7) or an opioid derivative, such Dextromethorphan (8) or a glycylamide, such as Remacemide (9) or a piperidinylethanol, such as Ifenprodil (10) or a piperidinylethanol, such as Eliprodil (11) or a diguanidine, such as Eliprodil (11a) or a γ-aminobutyric acid derivative, such as Gabapentin (46) or a polycyclic amine, such as Pizotyline (60) or derivatives of any of the above which are non-competitive NMDA antagonists or prodrugs thereof.

22. A method according to claim 16, wherein the substance is a non-NMDA glutamate receptor antagonist.

23. A method according to claim 22, wherein the substance is a competitive non-NMDA glutamate receptor antagonist.

24. A method according to claim 22, wherein the substance is a non-competitive non-NMDA glutamate receptor antagonist.

25. A method according to claim 17, wherein the substance is a tricyclic antidepressivum, such as Mirtazaprine (4d) or Venlafaxin (4e) or derivatives of any of the above which are NMDA glutamate receptor antagonists or prodrugs thereof.

26. A method according to claim 17, wherein the substance is a γ-aminobutyric acid derivative, such as Gabapentin (46), or a polycyclic amine, such as Pizotyline (60) or derivatives of any of the above which are NMDA glutamate receptor antagonists or prodrugs thereof.

27. A method according to claim 22, wherein the substance is an AMPA glutamate receptor antagonist.

28. A method according to claim 27, wherein the substance is a competitive AMPA glutamate receptor antagonist.

29. A method according to claim 28, wherein the substance is a quinoxalinedione, such as CNQX (19) or NBQX (20) or PNQX (21) or YM90K (22) or a dihydroquinolone, such as L-698,544 (23) or a diacidic decahydroisoquinoline, such as LY 215490 (24) or an amino acid isoxazole, such as AMOA (25) or an indoleoxime, such as NS-257 (26) or derivatives of any of the above which are competitive AMPA receptor antagonists or prodrugs thereof.

30. A method according to claim 27, wherein the substance is a non-competitive AMPA glutamate receptor antagonist.

31. A method according to claim 30, wherein the substance is a 2,3-benzodiazepine, such as GYKI 52466 (27) or a phthalazine, such as SYM 2206 (28) or derivatives of any of the above which are non-competitive AMPA receptor antagonists or prodrugs thereof.

32. A method according to claim 22, wherein the substance is a kainic acid receptor antagonist.

33. A method according to claim 32, wherein the substance is a competitive kainic acid receptor antagonist.

34. A method according to claim 33, wherein the substance is an indoleoxime, such as NS-102 (29) or derivatives thereof which are competitive kainic acid receptor antagonists or prodrugs thereof.

35. A method according to claim 32, wherein the substance is a non-competitive kainic acid receptor antagonist.

36. A method according to claim 22, wherein the substance is a metabotropic glutamate receptor antagonist.

37. A method according to claim 36, wherein the substance is a competitive metabotropic glutamate receptor antagonist.

38. A method according to claim 36, wherein the substance is a non-competitive metabotropic glutamate receptor antagonist.

39. A method according to claim 15, wherein the substance is a metabotropic glutamate receptor agonist.

40. A method according to claim 39, wherein the substance is a phenylglycine, such as 4CPG (30) or an amino acid indane, such as UPF523 (31) or a phosphono amino acid, such as L-AP4 (32) or derivatives of any of the above which are metabotropic glutamate receptor agonists or prodrugs thereof.

41. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of 5-HT or substantially blocking the release of 5-HT or substantially counteracting the action of 5-HT or substantially blocking 5-$HT_{2,3}$ receptors.

42. A method according to claim 41 or 14, wherein the substance is a 5-$HT_{2,3}$ receptor antagonist.

43. A method according to claim 42, wherein the substance is a tropan derivative, such as Tropanserin (59) or a polycyclic amine, such as Pizotyline (60) or derivatives of any of the above which are 5-$HT_{2,3}$ receptor antagonists or prodrugs thereof.

44. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially enhancing the production of GABA or substantially enhancing the release of GABA or substantially enhancing the action of GABA or substantially activating receptors for GABA.

45. A method according to claim 44, wherein the substance is a GABA activity enhancer.

46. A method according to claim 45, wherein the substance is a benzodiazepine, such as Midazolam (49a) or derivatives thereof which are GABA activity enhancers or prodrugs thereof.

47. A method according to claim 44 or 14, wherein the substance is a GABA uptake inhibitor.

48. A method according to claim 47, wherein the substance is a carboxypiperidine derivative, such as (±)-*cis*-4-Hydroxynipecotic acid (50) or a carboxypyridine derivative, such as Guvacine (51) or a 3-hydroxyisoxazole, such as THPO (52) or a nipecotic acid derivative, such as SKF 89976-A (53) or Tiagabine (54) or a guvacine derivative, such as NO-711 (54a) or derivatives of any if the above which are GABA uptake inhibitors or prodrugs thereof.

49. A method according to claim 44, wherein the substance is a GABA-A agonist.

50. A method according to claim 49, wherein the substance is a γ-aminobutyric acid derivative, such as Gabapentin (46) or TACA (46A) or Isonipecotic acid (47) or Isoguvacine (48) or a 3-hydroxyisoxazole, such as THIP (49) or derivatives of any of the above which are GABA-A agonists or prodrugs thereof.

51. A method according to claim 44, wherein the substance is a GABA transaminase inhibitor.

52. A method according to claim 51, wherein the substance is a γ-aminobutyric acid derivative, such as Vigabatrin (55) or derivatives thereof which are GABA transaminase inhibitors or prodrugs thereof.

53. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of substance P or substantially blocking the release of substance P or substantially counteracting the action of substance P or substantially blocking receptors for substance P.

54. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of nitric oxide or substantially counteracting the action of nitric oxide or substantially blocking the production of nitric oxide synthase (NOS) or substantially counteracting the action of nitric oxide synthase (NOS).

55. A method according to claim 54 or 14, wherein the substance is a nitric oxide inhibitor.

56. A method according to claim 54 or 55, wherein the substance is an NOS inhibitor.

57. A method according to claim 56, wherein the substance is an arginine derivative, such as L-NAME (41) or L-NMMA (41a) or L-NIO (41b) or L-NNA (41c) or Dimethyl-L-arginine (41d) or a citrulline derivative, such as Thiocitrulline (42) or (S)-Methylthiocitrulline (42a) or an indazole, such as 7-Nitroindazole (43) or an imidazolin-N-oxide, such as Potassium carboxy-PTIO (44) or a phenylimidazole, such as TRIM (44a) or a 21-aminosteroid, such as Tirilazad (44b) or a biphenyl, such as Diphenyleneiodinium chloride (44c) or a piperidine derivative, such as Paroxetine (44d) or derivatives of any of the above which are NOS inhibitors or prodrugs thereof.

58. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of guanylate cyclase or substantially counteracting the action of guanylate cyclase or substantially blocking the production of cyclic guanylate monophosphate (cGMP) or substantially counteracting the action of cyclic guanylate monophosphate (cGMP) or substantially blocking any further steps in the reaction induced by cyclic guanylate monophosphate (cGMP).

59. A method according to claim 58 or 14, wherein the substance is a guanylate cyclase inhibitor.

60. A method according to claim 59, wherein the substance is a quinoxaline, such as ODQ (45) or derivatives thereof which are guanylate cyclase inhibitors.

61. A method according to claim 58, wherein the substance is a cGMP inhibitor.

62. A method according to claim 58, wherein the substance is capable of substantially counteracting the action of protein kinase C.

63. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of CGRP or substantially blocking the release of CGRP or substantially counteracting the action of CGRP or substantially blocking receptors for CGRP.

64. A method according to claim 63 or 14, wherein the substance is a CGRP inhibitor.

65. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of neurokinin A or substantially blocking the release of neurokinin A or substantially counteracting the action of neurokinin A or substantially blocking receptors for neurokinin A, with the proviso that the substace is not a 3-benzylamino-2-phenylpiperidine as disclosed in WO 96/29326 or an arylglycinamide derivative as disclosed in WO 96/32386.

66. A method according to claim 65, wherein the substance is an NK1 receptor antagonist.

67. A method according to claim 66, wherein the substance is an androstane, such as WIN 51,708 (33) or a peptidomimetic, such as LY 303870 (34) or a piperidinamine, such as CP 99,994 (35) or a peptidomimetic, such as FK 888 (36) or derivatives of any of the above which are NK1 receptor antagonists or prodrugs thereof.

68. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of neurokinin B or substantially blocking the release of neurokinin B or substantially counteracting the action of neurokinin B or substantially blocking receptors for neurokinin B, with the proviso that the substance is not an arylglycinamide derivative as disclosed in WO 96/32386.

69. A method according to claim 68, wherein the substance is an NK2 receptor antagonist.

70. A method according to claim 69, wherein the substance is a peptidomimetic, such as SR-48968 **(37)** or a peptidomimetic, such as GR 159897 **(38)** or derivatives thereof which are NK2 receptor antagonists or prodrugs thereof.

71. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of bradykinin or substantially blocking the release of bradykinin or substantially counteracting the action of bradykinin or substantially blocking receptors for bradykinin.

72. A method according to claim 71 or 14, wherein the substance is a bradykinin antagonist.

73. A method according to claim 72, wherein the substance is a peptidomimetic, such as Icatibant **(39)** or WIN 64338 **(40)** or derivatives of any of the above which are bradykinin receptor antagonists or prodrugs thereof.

74. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of PACAB or substantially blocking the release of PACAB or substantially counteracting the action of PACAB or substantially blocking receptors for PACAB.

75. A method according to claim 74 or 14, wherein the substance is a PACAB inhibitor.

76. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of adenosine or substantially blocking the release of adenosine or substantially counteracting the action of adenosine or substantially blocking adenosine A2 receptors.

77. A method according to claim 76 or 14, wherein the substance is an A2 receptor antagonist.

78. A method according to claim 77, wherein the substance is a xanthine derivative, such as DMPX **(57)** or derivatives thereof which are A2 receptor antagonists or prodrugs thereof.

79. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially enhancing the production of adenosine or substantially enhancing the release of adenosine or substantially enhancing the action of adenosine or substantially activating adenosine A1 receptors.

80. A method according to claim 79, wherein the substance is an adenosine uptake inhibitor.

81. A method according to claim 80, wherein the substance is a pyrimidine derivative, such as Dipyridamole **(56b)** or derivatives thereof ehich are adenosine uptake inhibitors or prodrugs thereof.

82. A method according to claim 79 or 14, wherein the substance is an A1 receptor agonist.

83. A method according to claim 82, wherein the substance is an adenosine derivative, such as $N^6$-Cyclopentyladenosine **(56)** or an adeninglucoside, such as Adenosine **(56a)** or derivatives thereof which are A1 receptor agonists or prodrugs thereof.

84. A method according to claim 79, wherein the substance is an adenosine uptake inhibitor.

85. A method according to claim 84, wherein the substance is a homopiperazine derivative, such as Dilazep **(58)** or derivatives thereof which are adenosine uptake inhibitors or prodrugs thereof.

86. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially enhancing the production of galanine or substantially enhancing the release of galanine or substantially enhancing the action of galanine or substantially activating receptors for galanine.

87. A method according to claim 86 or 14, wherein the substance is a galanine receptor agonist.

88. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially enhancing the production of norepinephrine or substantially enhancing the release of norepinephrine or substantially enhancing the action of norepinephrine or substantially activating receptors for norepinephrine.

89. A method according to claim 88 or 14, wherein the substance is an norepinephrine receptor agonist.

90. A method according to claim 89, wherein the substance is an α-2 receptor agonist.

91. A method according to claim 90, wherein the substance is an aminoimidazoline, such as Clonidine (61) or an aminoimidazoline, such as Apraclonidine (62) or a thiazinamine, such as Xylazine (63) or an imidazole, such as Dexmedetomidine (64) or derivatives of any of the above which are α-2 receptor agonists or prodrugs thereof.

92. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of glycine or substantially blocking the release of glycine or substantially counteracting the action of glycine or substantially blocking receptors for glycine.

93. A method according to claim 92 or 14, wherein the substance is a glycine antagonist.

94. A method according to claim 93, wherein the substance is an aminopyrrolidinone, such as (*R*)-HA-966 (12) or a kynurenic acid derivative, such as 7-Cl-Kynurenic acid (13) or a tetrahydroquinoline, such as L-689,560 (14) or a kynurenic acid derivative, such as L-701,252 (14a) or L-701,273 (14b) or L-701,324 (14c) or an indole such as GV150526A (14d) or a glycine derivative, such as ACPC (15) or a quinoxalinedione, such as MNQX (16) or ACEA 1021 (17) or a quinoxalinedione, such as DCQX (17a) or a dicarbamate, such as Felbamate (18) or derivatives of any of the above which are glycine antagonists or prodrugs thereof.

95. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of histamin or substantially blocking the release of histamin or substantially counteracting the action of histamin or substantially blocking receptors for histamin.

96. A method according to claim 5 or 10, wherein the substance is a substance which, in the peripheral and/or central nervous system, is capable of substantially blocking the production of neurotrophins or substantially blocking the release of neurotrophins or substantially counteracting the action of neurotrophins or substantially blocking receptors for neurotrophins.

97. A method according to claim 96 or 14, wherein the substance is an neurotrophin receptor antagonist.

98. A method according to claim 5 or 10, wherein the substance is capable of substantially blocking $Na^+$ ion channels in the peripheral and/or central nervous system.

99. A method according to claim 98 or 14, wherein the substance is a $Na^+$ channel blocker.

100. A method according to claim 99, wherein the substance is a triazine, such as Lamotrigine (65) or a diphenylmethylpiperazine, such as Lifarizine (66) or a hydantoin, such as Phenytoin (67) or an aminopiperidine, such as Lubeluzole (68) or a benzthiazole, such as Riluzole (69) or a dibenzazepine, such as Carbamazepine (70) or a phenylamide, such as Lidocaine (71) or a phenylamide, such as Tocainide (72) or a aminoethylanisole, such as Mexiletene (73) or derivatives of any of the above which are $Na^+$ channel blockers or prodrugs thereof.

101. A method according to claim 5 or 10, wherein the substance is capable of substantially blocking $Ca^{2+}$ ion channels in the peripheral and/or central nervous system.

102. A method according to claim 101 or 14, wherein the substance is a $Ca^{2+}$ channel blocker..

103. A method according to claim 102, wherein the substance is a diphenylmethylpiperazine, such as Flunarizine (74) or an arylphosphonic ester, such as Fostedil (75) or derivatives of any of the above which are $Ca^{2+}$ channel blockers or prodrugs thereof.

104. A method of treatment of tension-type headache comprising administering to a person in need of such treatment an effective amount of a substance which substantially inhibits the action of the enzyme nitric oxide synthase (NOS) and thereby reduces chronic pain in connection with tension-type headache.

105. A method according to claim 104, wherein the substance is an arginine derivative, such as L-NAME (41) or L-NMMA (41a) or L-NIO (41b) or L-NNA (41c) or Dimethyl-L-arginine (41d) or a citrulline derivative, such as Thiocitrulline (42) or (S)-Methylthiocitrulline (42a) or an indazole, such as 7-Nitroindazole (43) or an imidazolin-N-oxide, such as Potassium carboxy-PTIO (44) or a phenylimidazole, such as TRIM (44a) or a 21-aminosteroid, such as Tirilazad (44b) or a biphenyl, such as Diphenyleneiodinium chloride (44c) or a piperidine derivative, such as Paroxetine (44d) or derivatives of any of the above which are NOS inhibitors or prodrugs thereof.

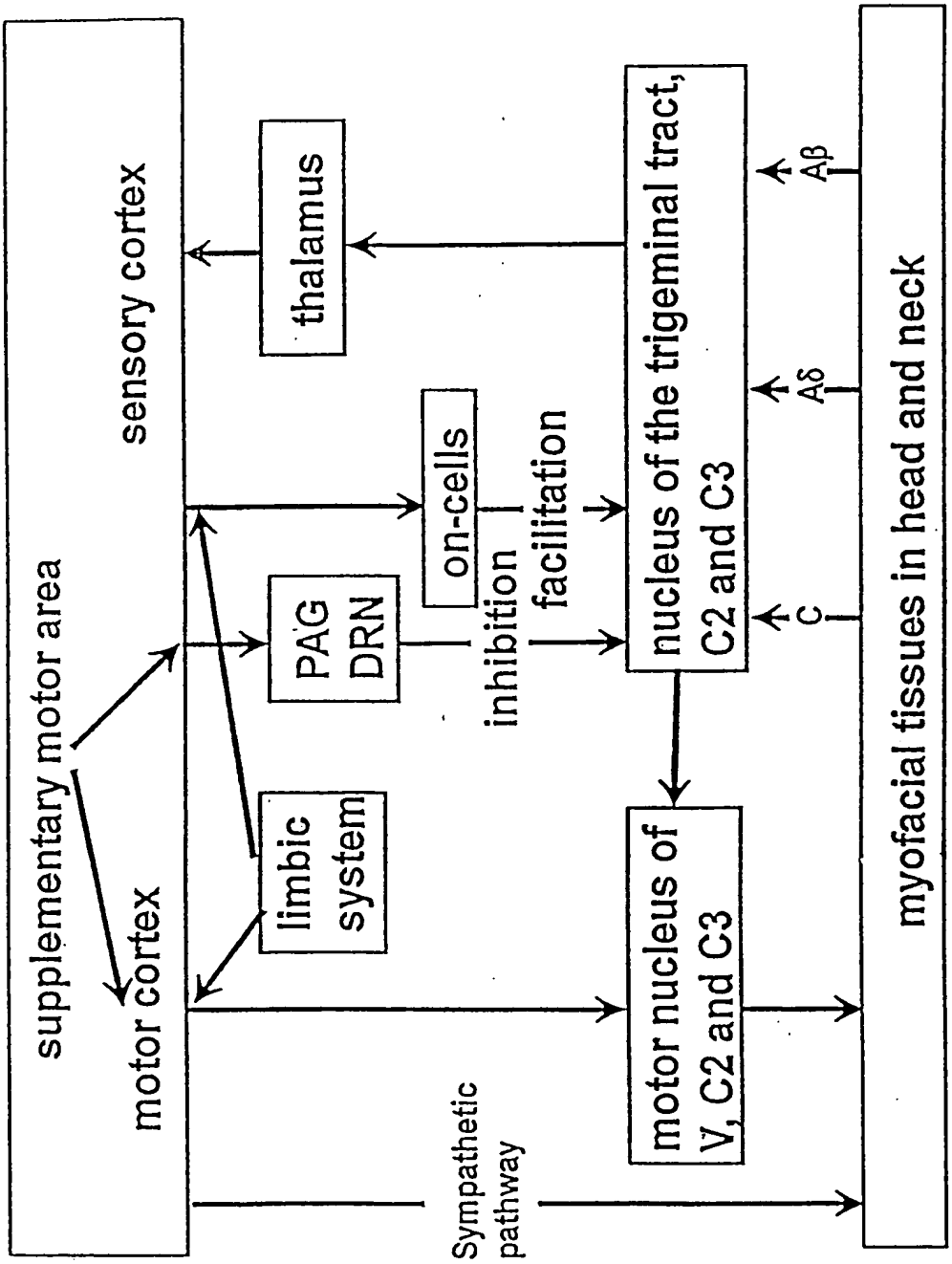


Fig. 1

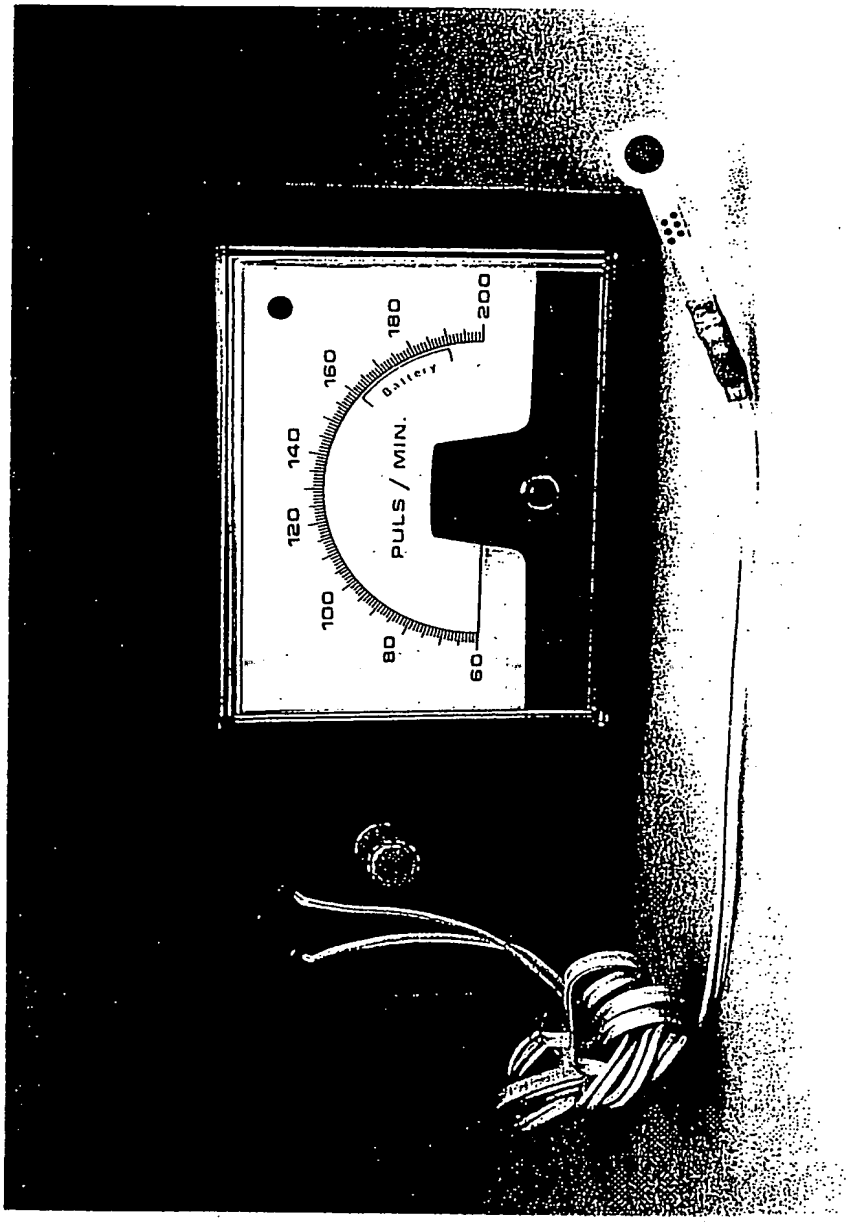


Fig. 2A

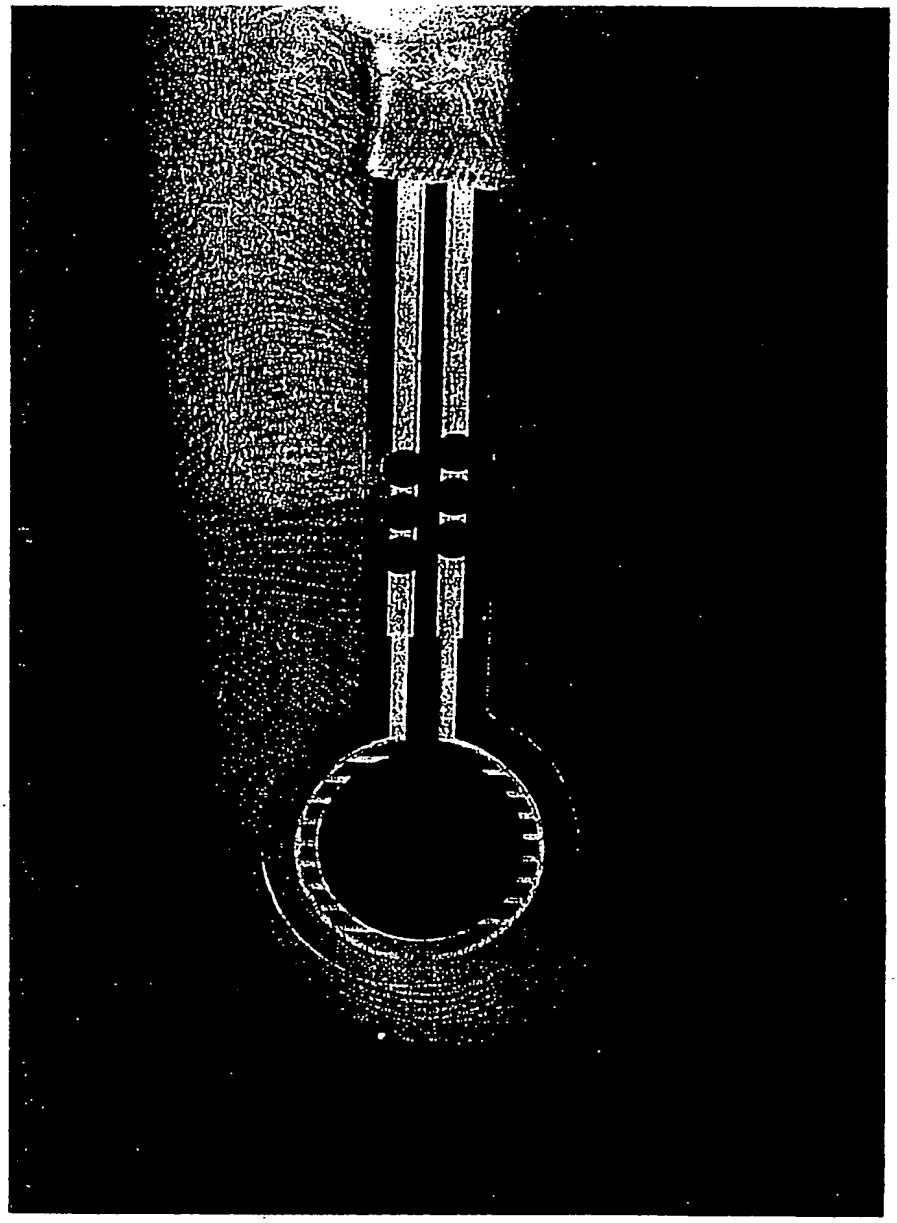

Fig. 2B

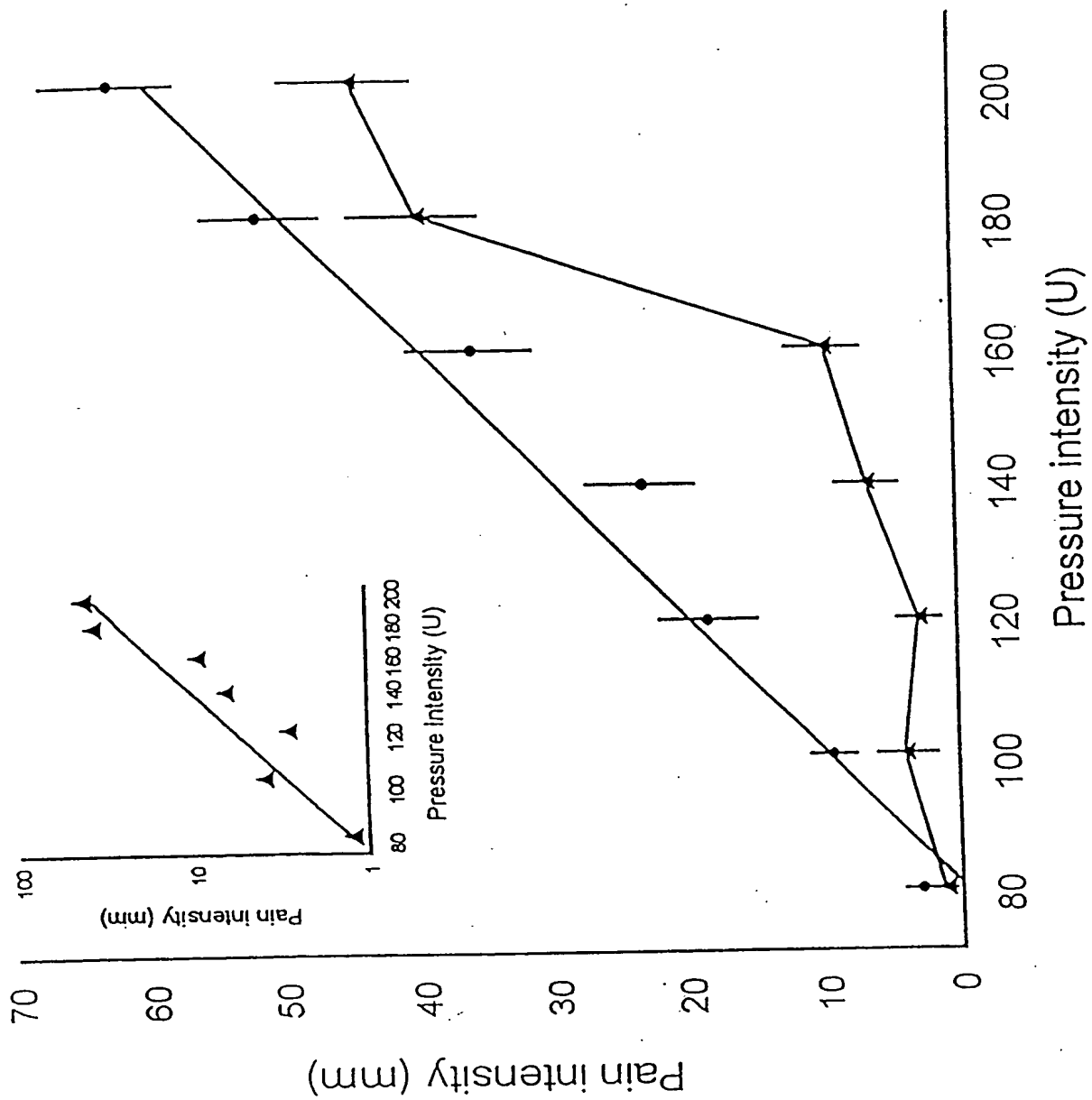


**Fig. 3**

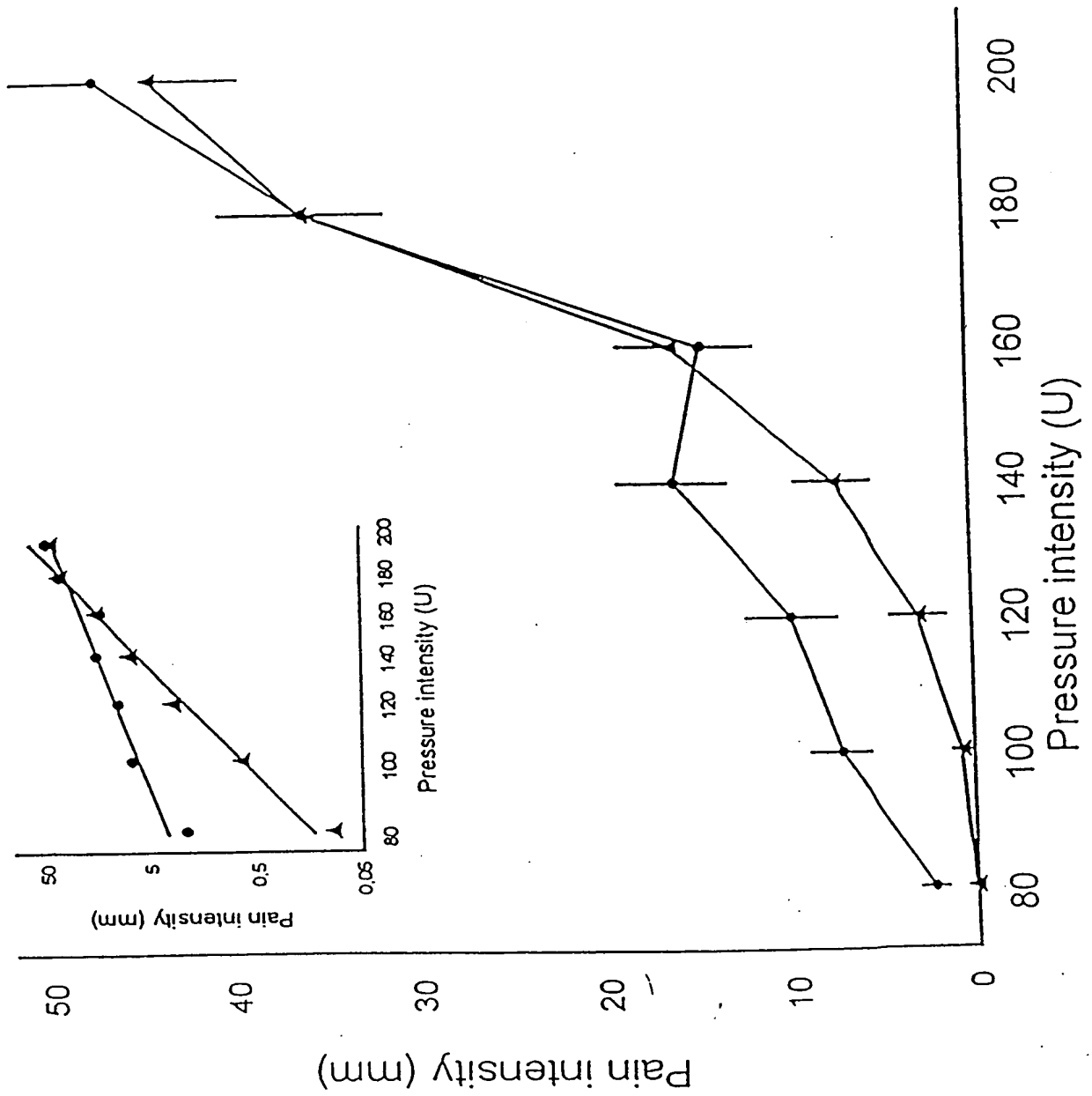


**Fig. 4**

SUBSTITUTE SHEET (RULE 26)

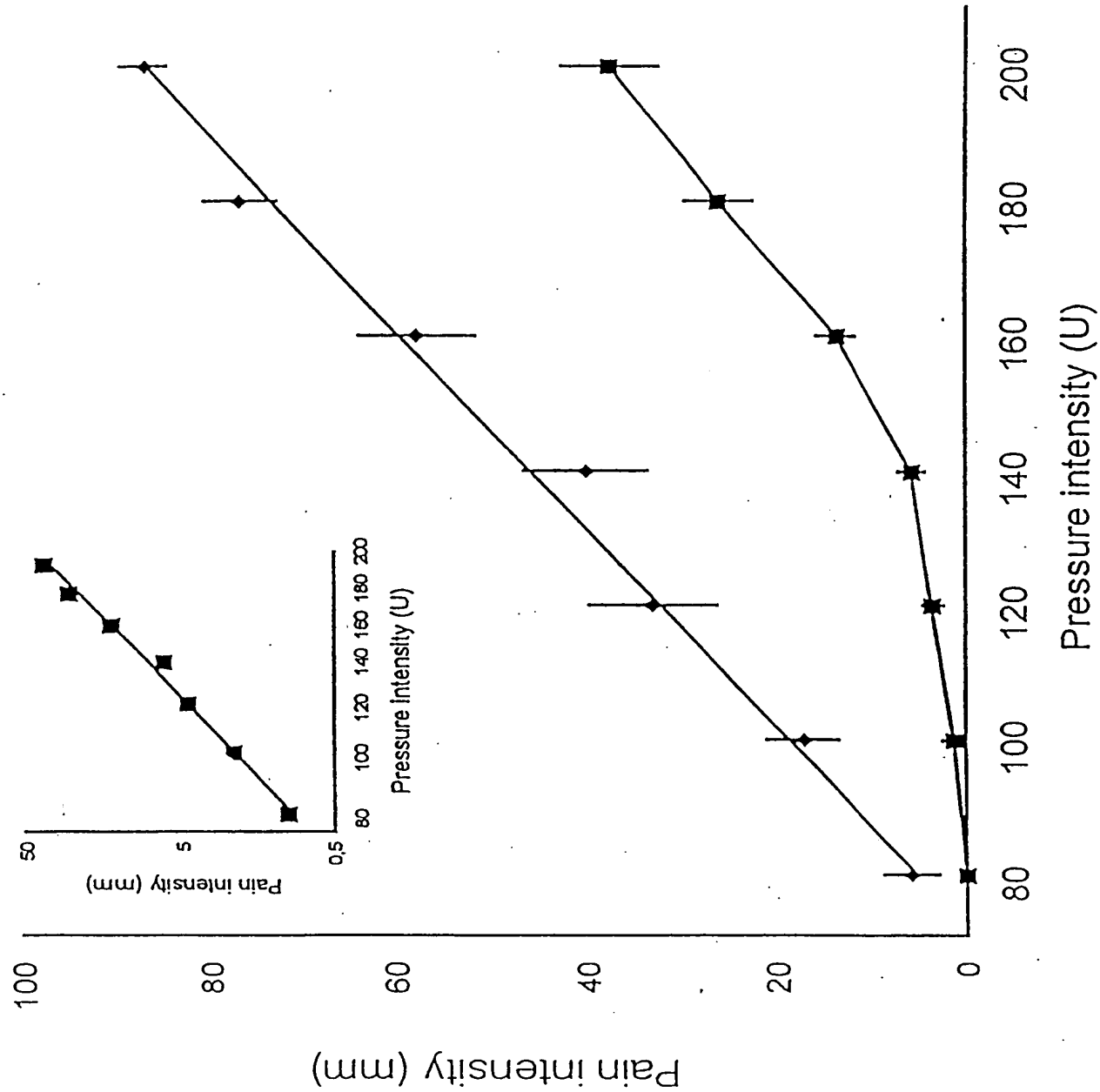


**Fig. 5**

SUBSTITUTE SHEET (RULE 26)

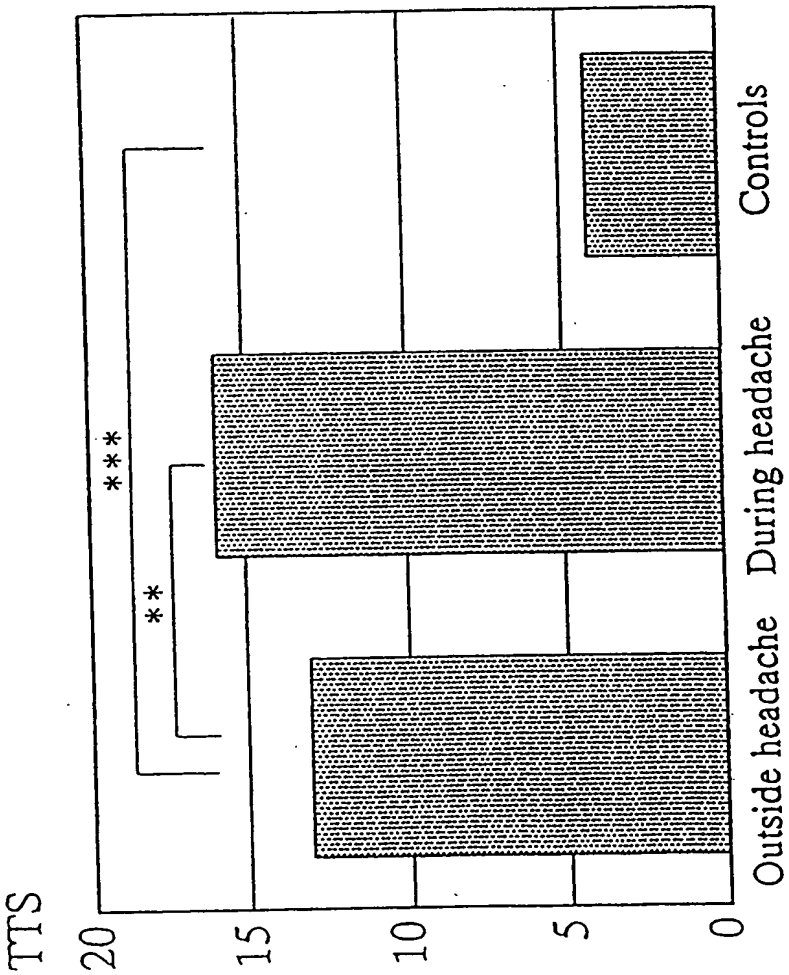


Fig. 6

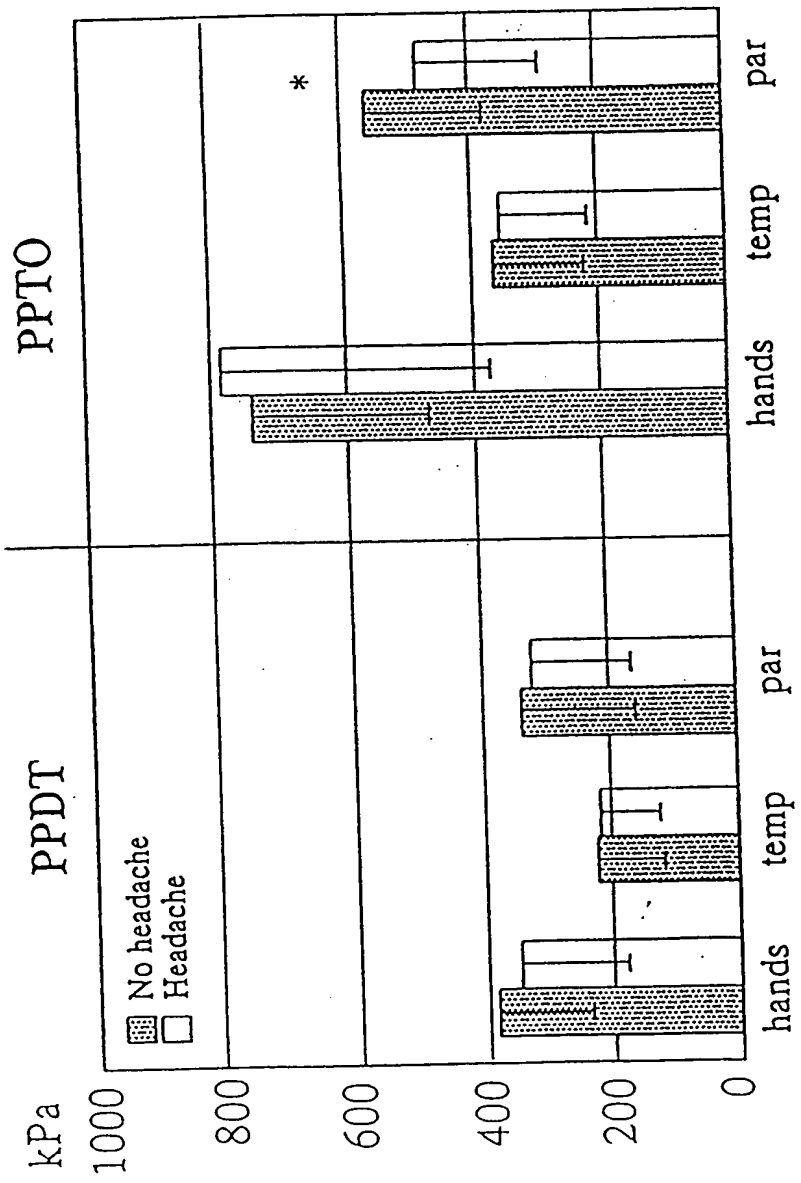
PPTO
PPDT
No headache
Headache
kPa
1000
800
600
400
200
0
hands
temp
par
hands
temp
par
*

Fig. 7

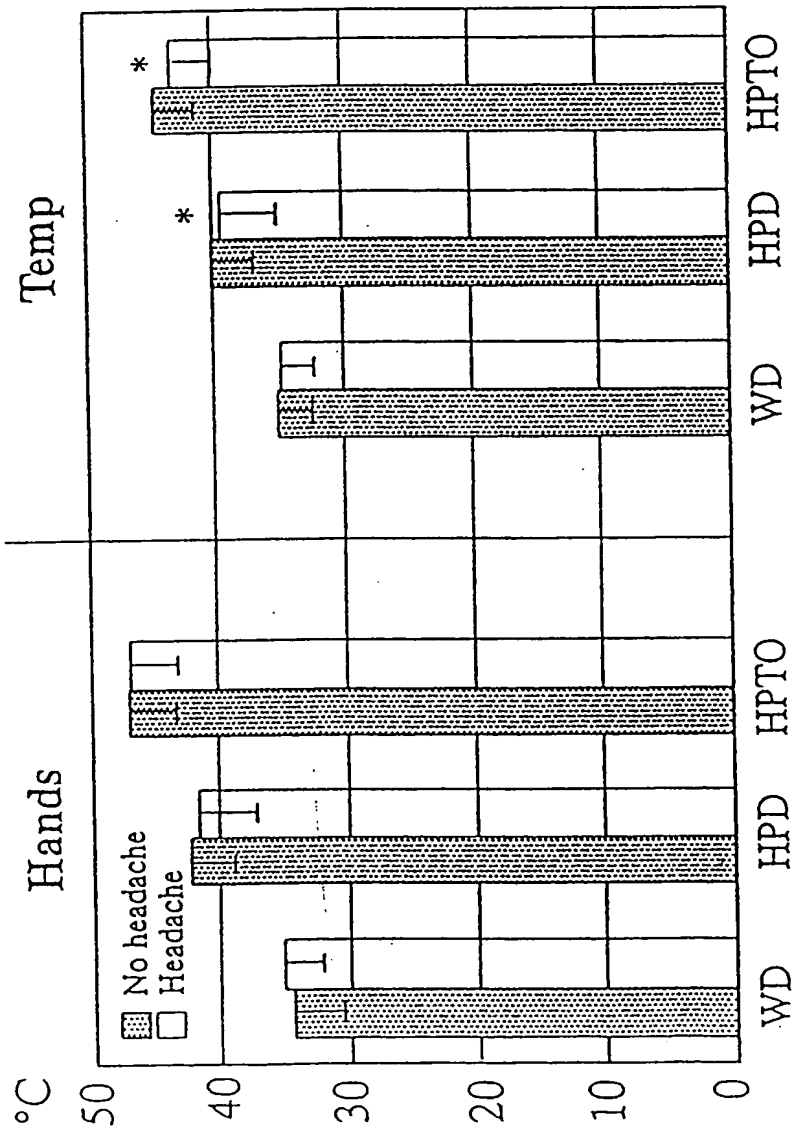


Fig. 8

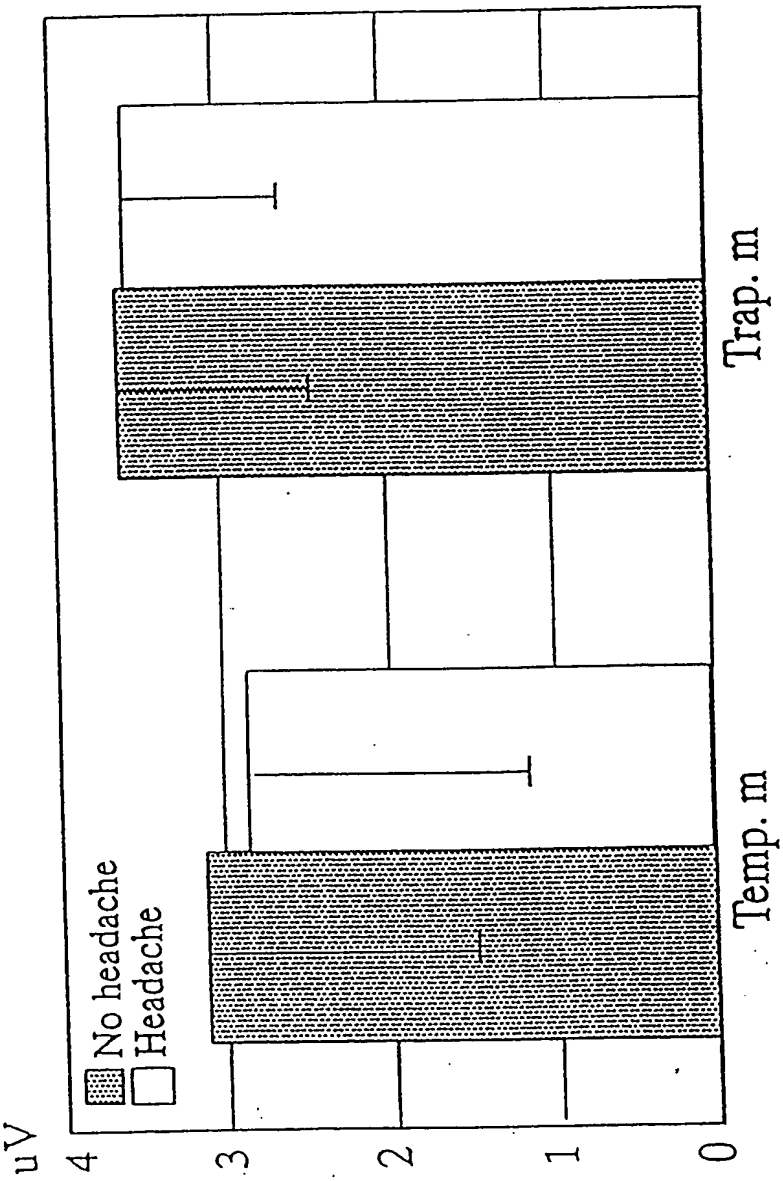


Fig. 9A

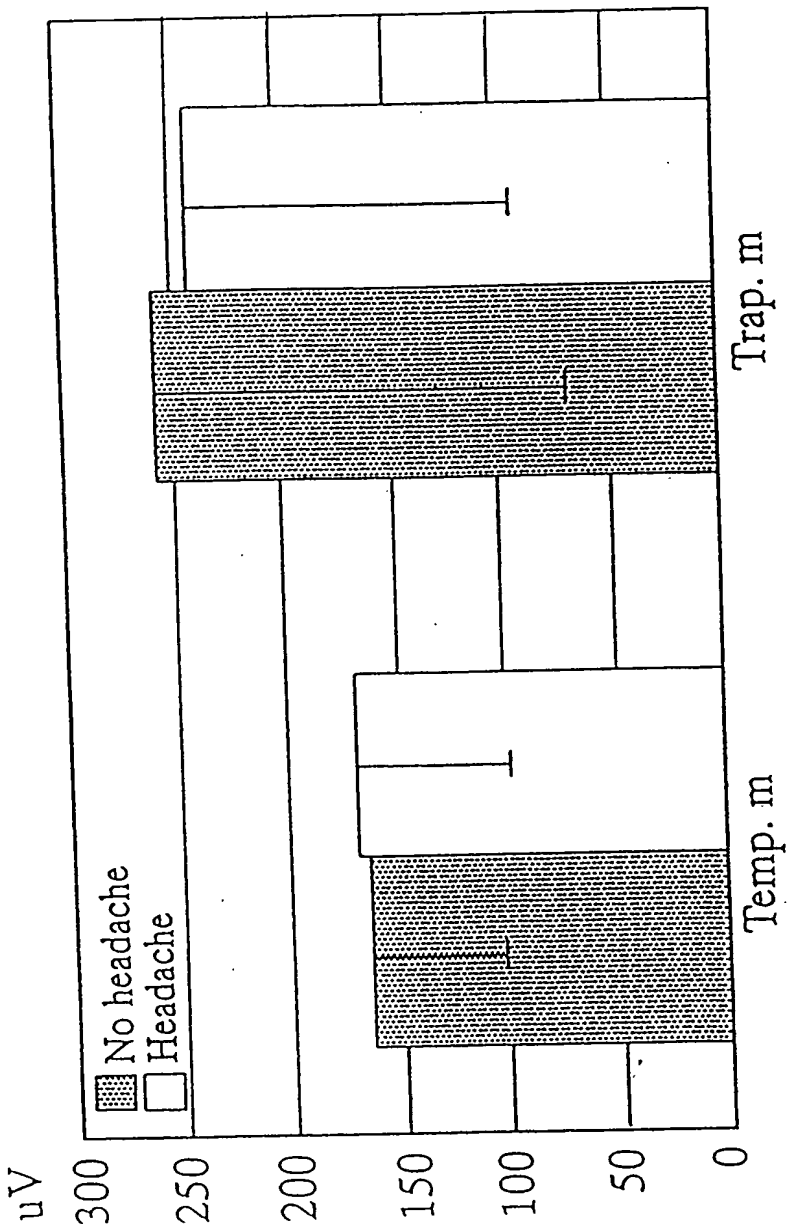


Fig. 9B

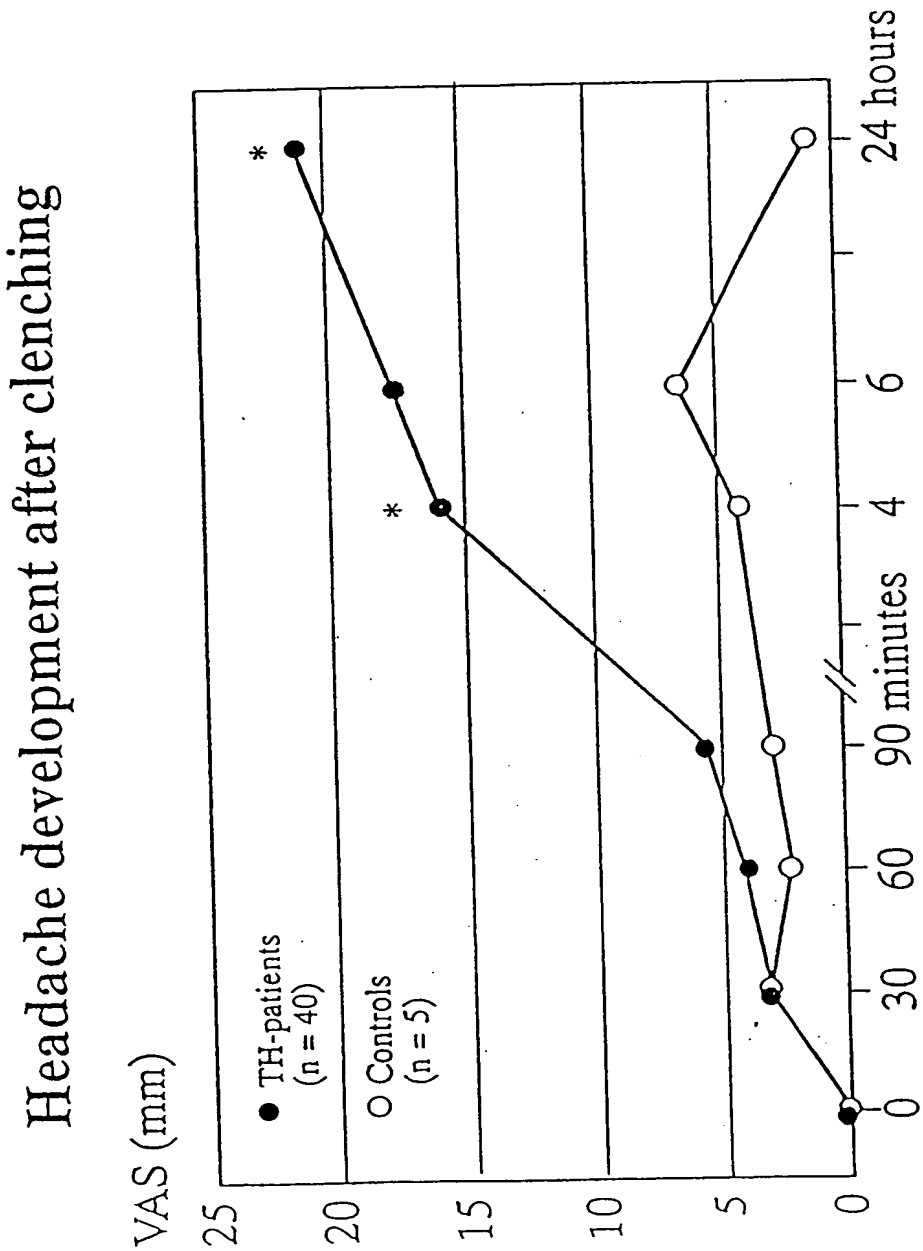


Fig. 10

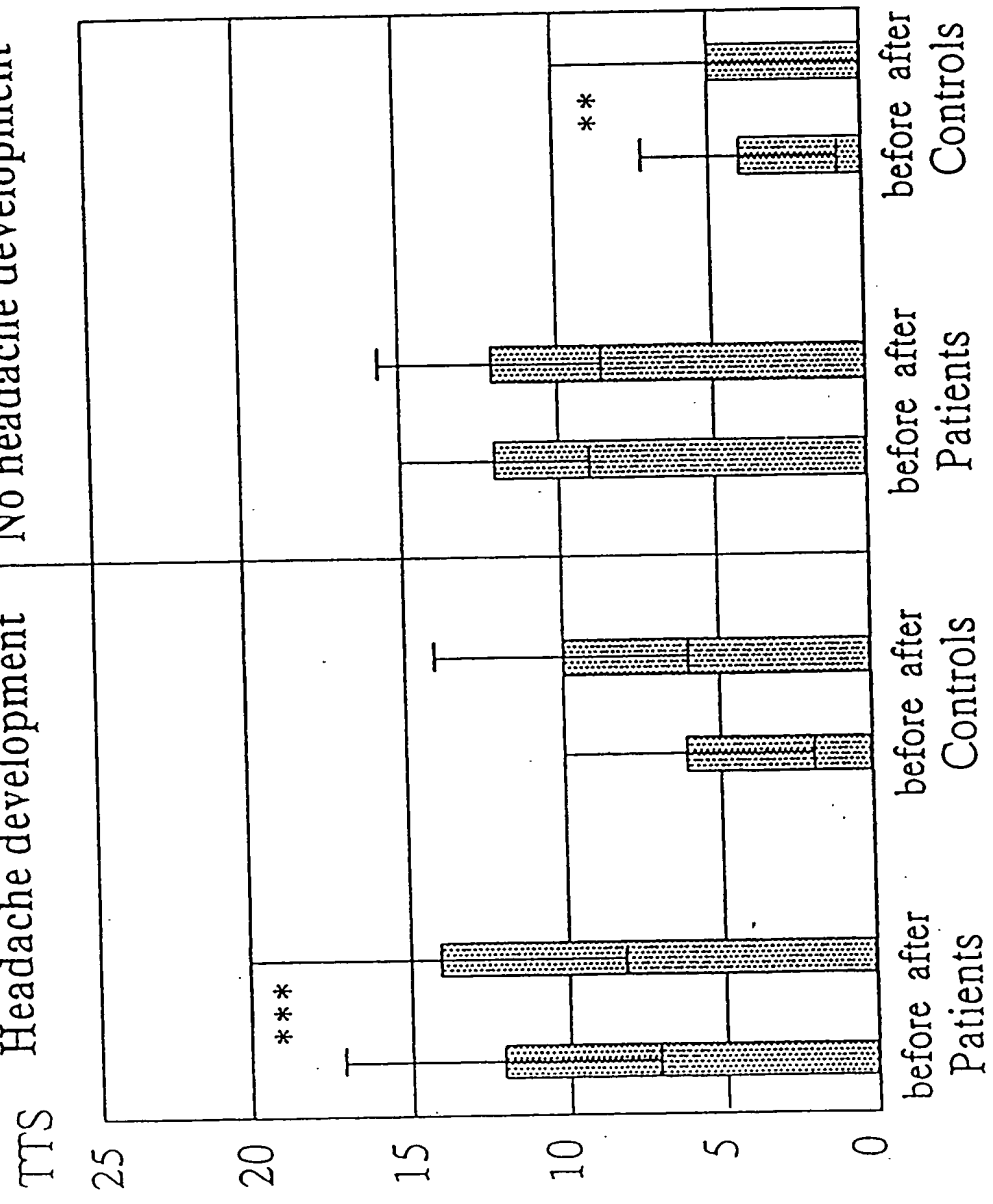


Fig. 11

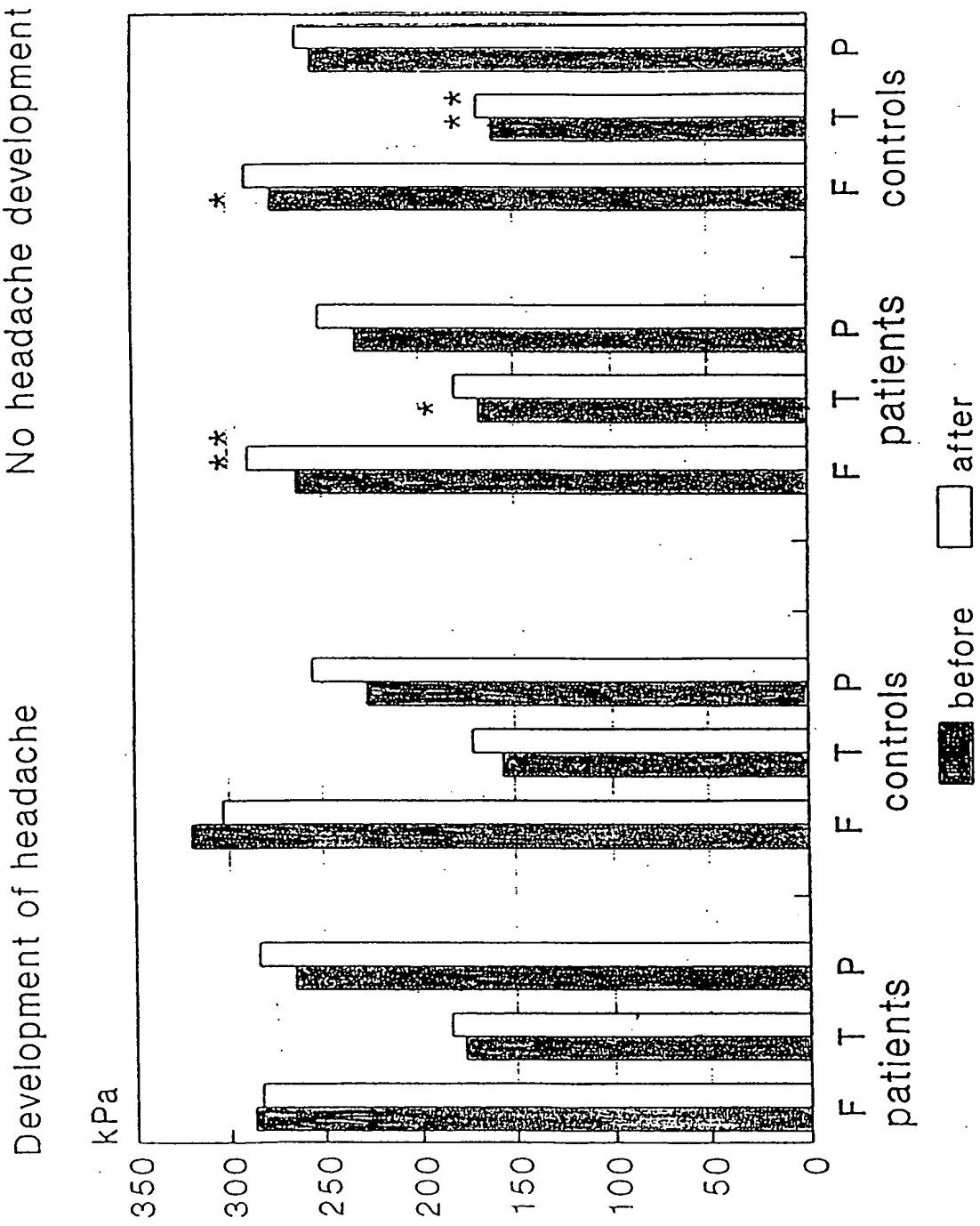


Fig. 12A

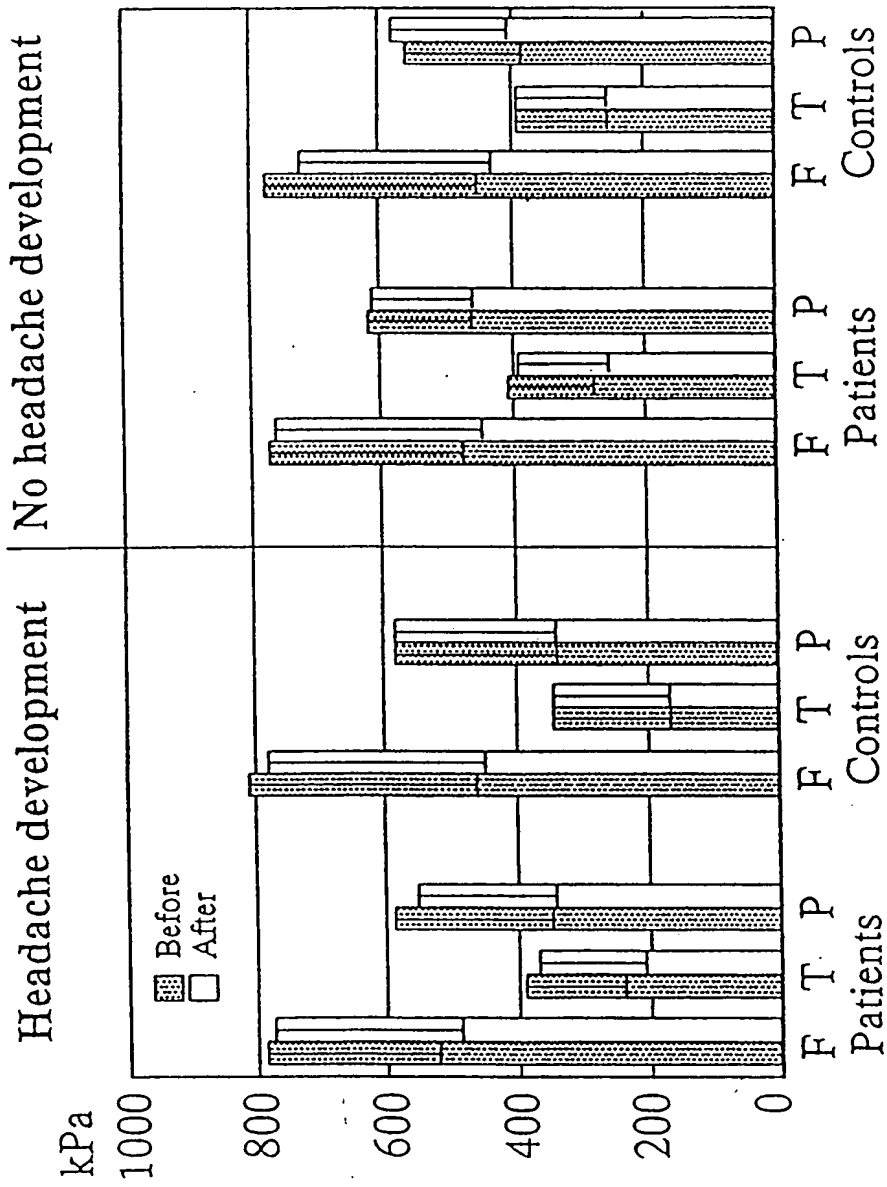
Headache development
No headache development
Before
After
kPa
1000
800
600
400
200
0
F T P
Patients
F T P
Controls
F T P
Patients
F T P
Controls

Fig. 12B

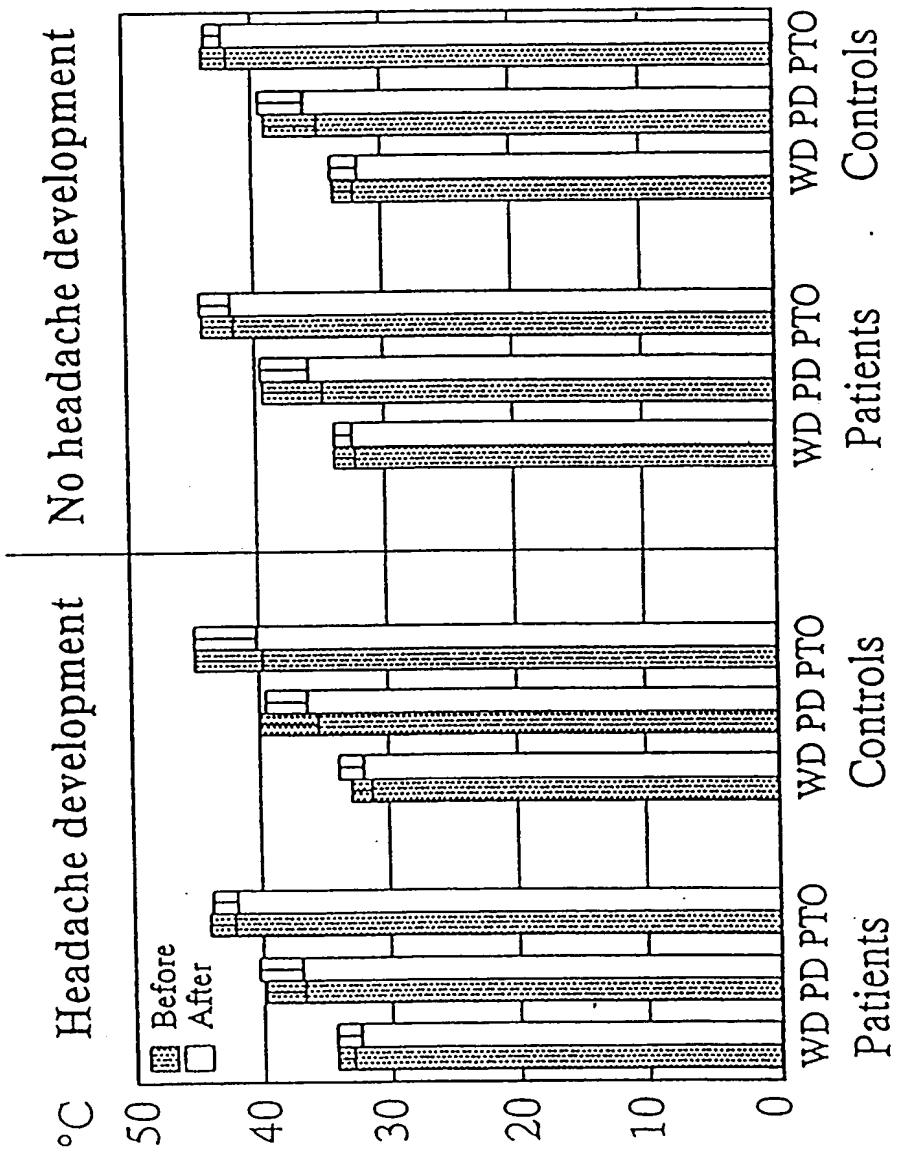
°C
50
40
30
20
10
0
Headache development
No headache development
Before
After
WD PD PTO
WD PD PTO
Patients
Controls
WD PD PTO
WD PD PTO
Patients
Controls

Fig. 13

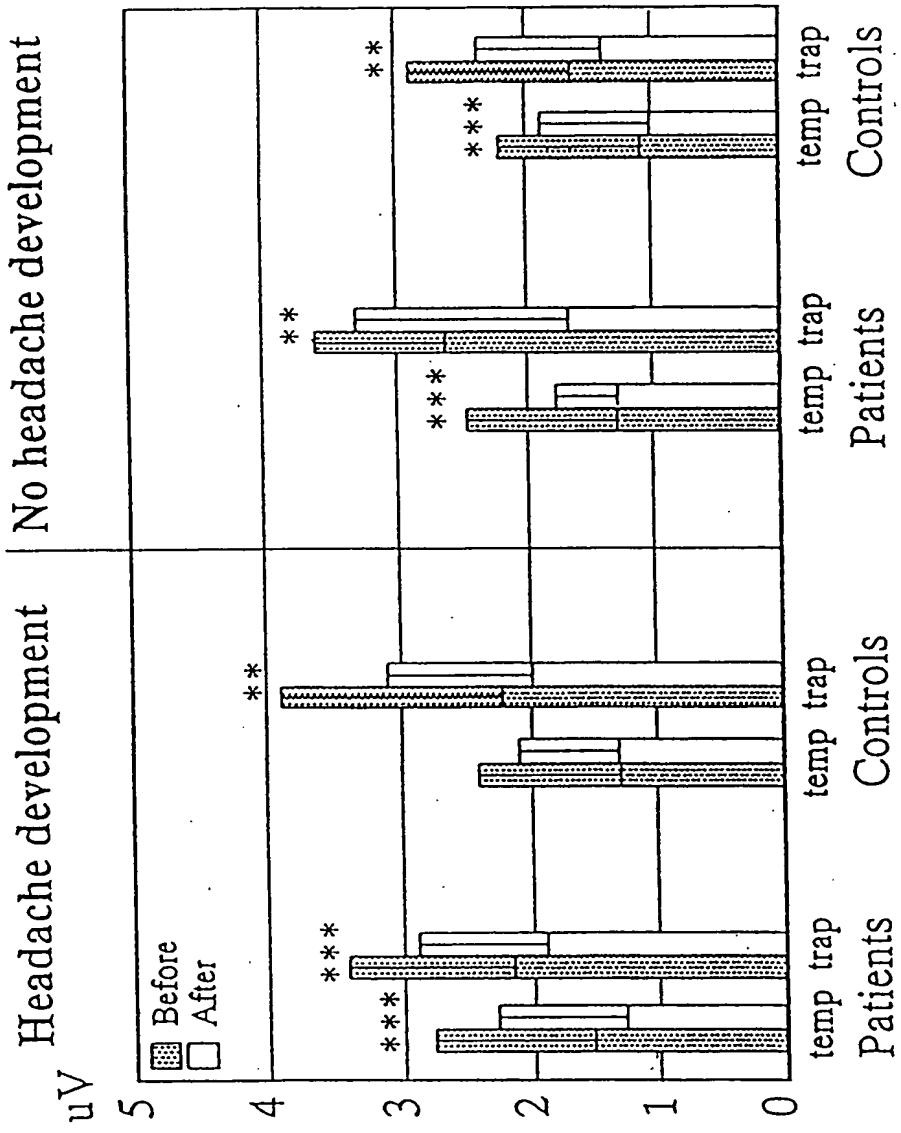
Headache development
No headache development
uV
5
4
3
2
1
0
Before
After
temp trap
Patients
Controls
temp trap
Patients
Controls
temp trap
Patients
Controls
temp trap
Patients
Controls

Fig. 14A

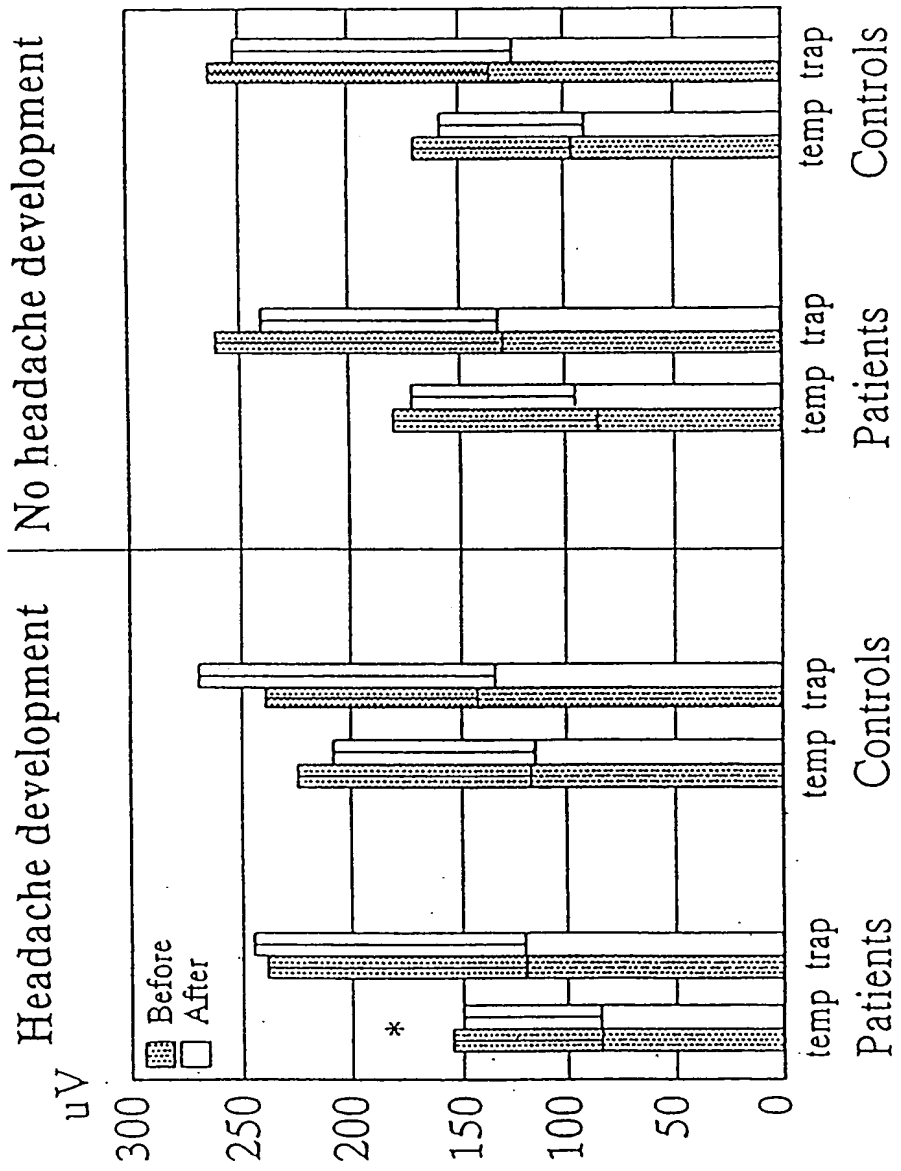
Headache development
No headache development
uV
300
250
200
150
100
50
0
Before
After
*
temp trap
Patients
temp trap
Controls
temp trap
Patients
temp trap
Controls

Fig. 14B

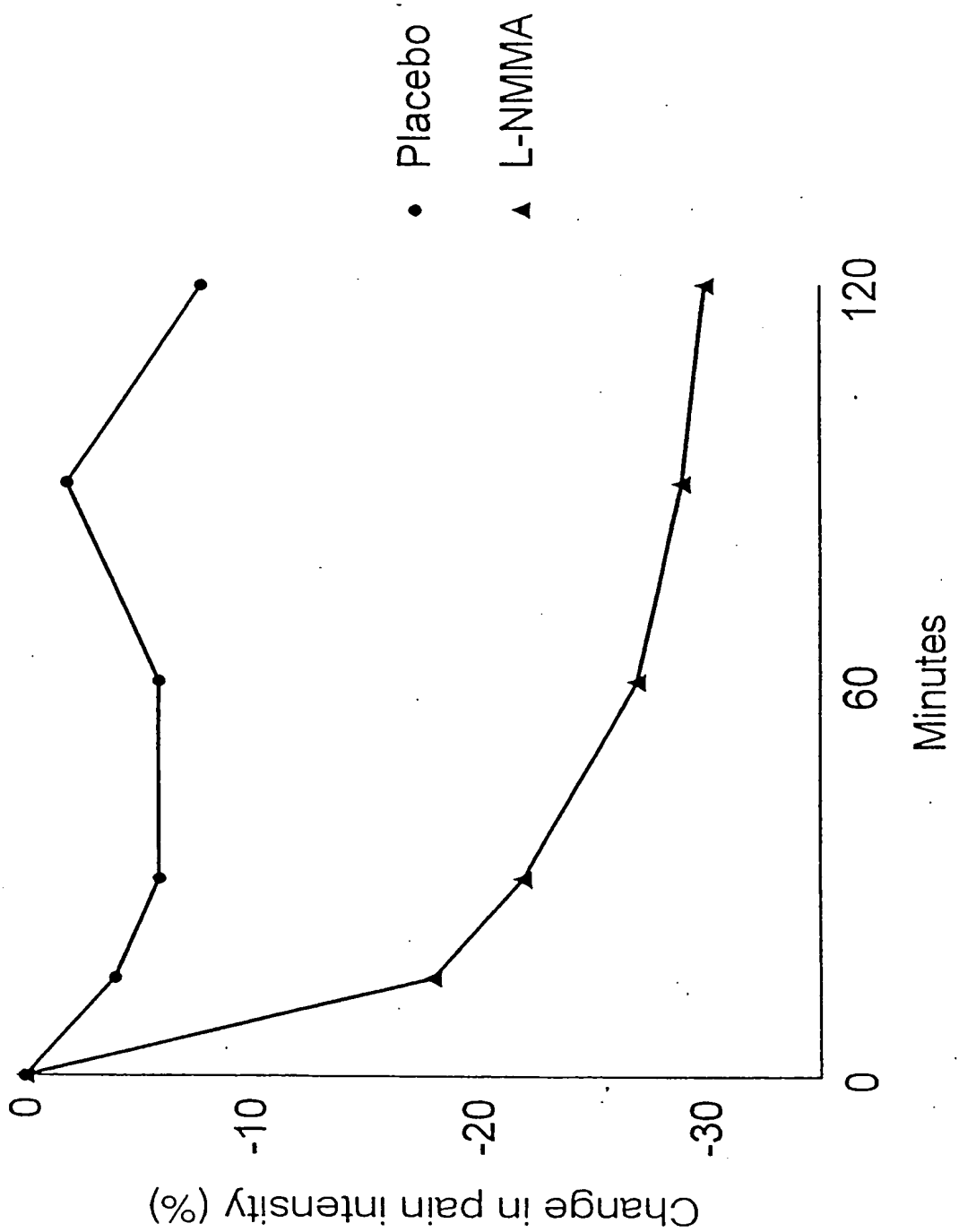
Placebo
L-NMMA
0
-10
-20
-30
Change in pain intensity (%)
0
60
120
Minutes

Fig. 15

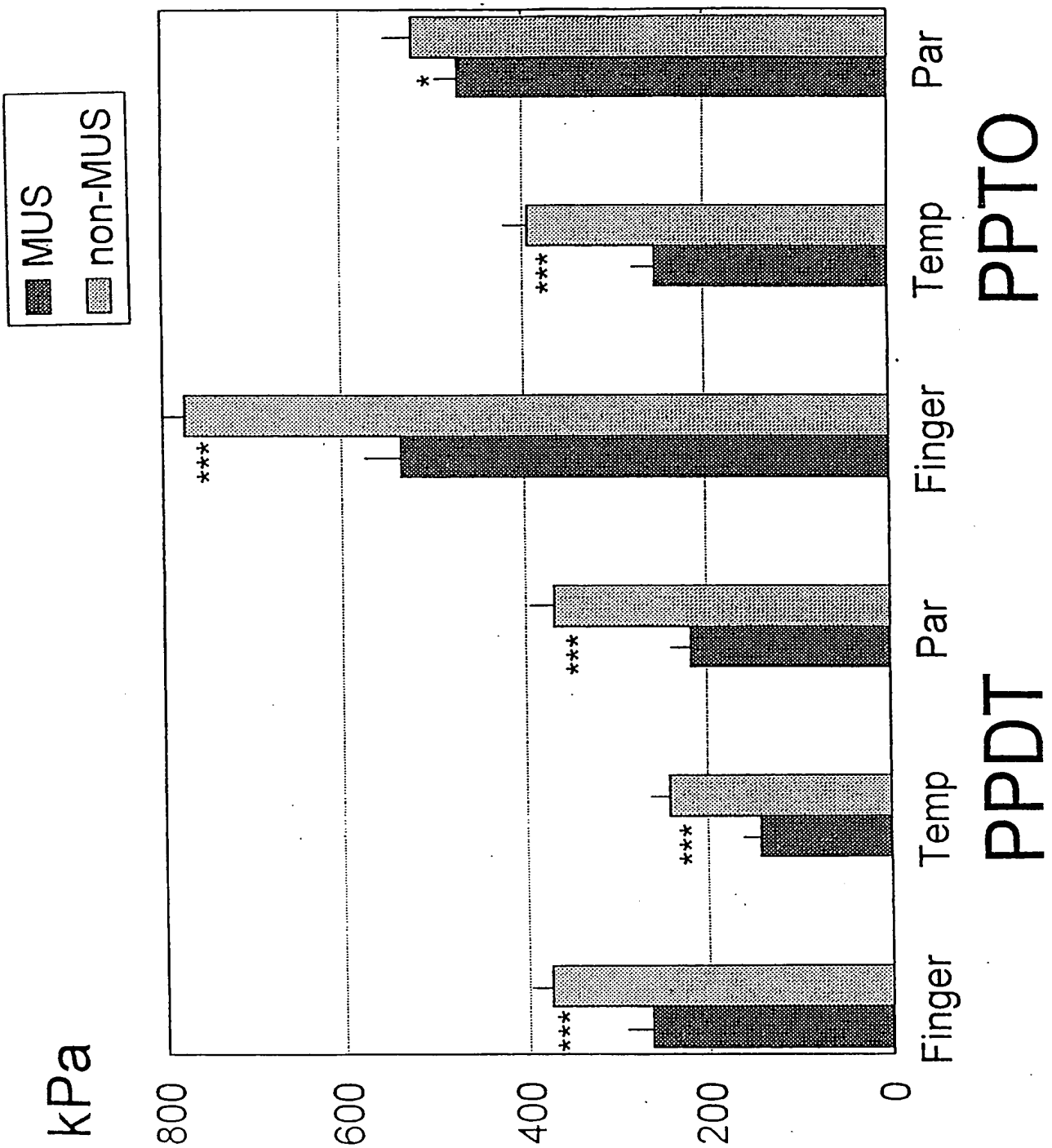


Fig. 16

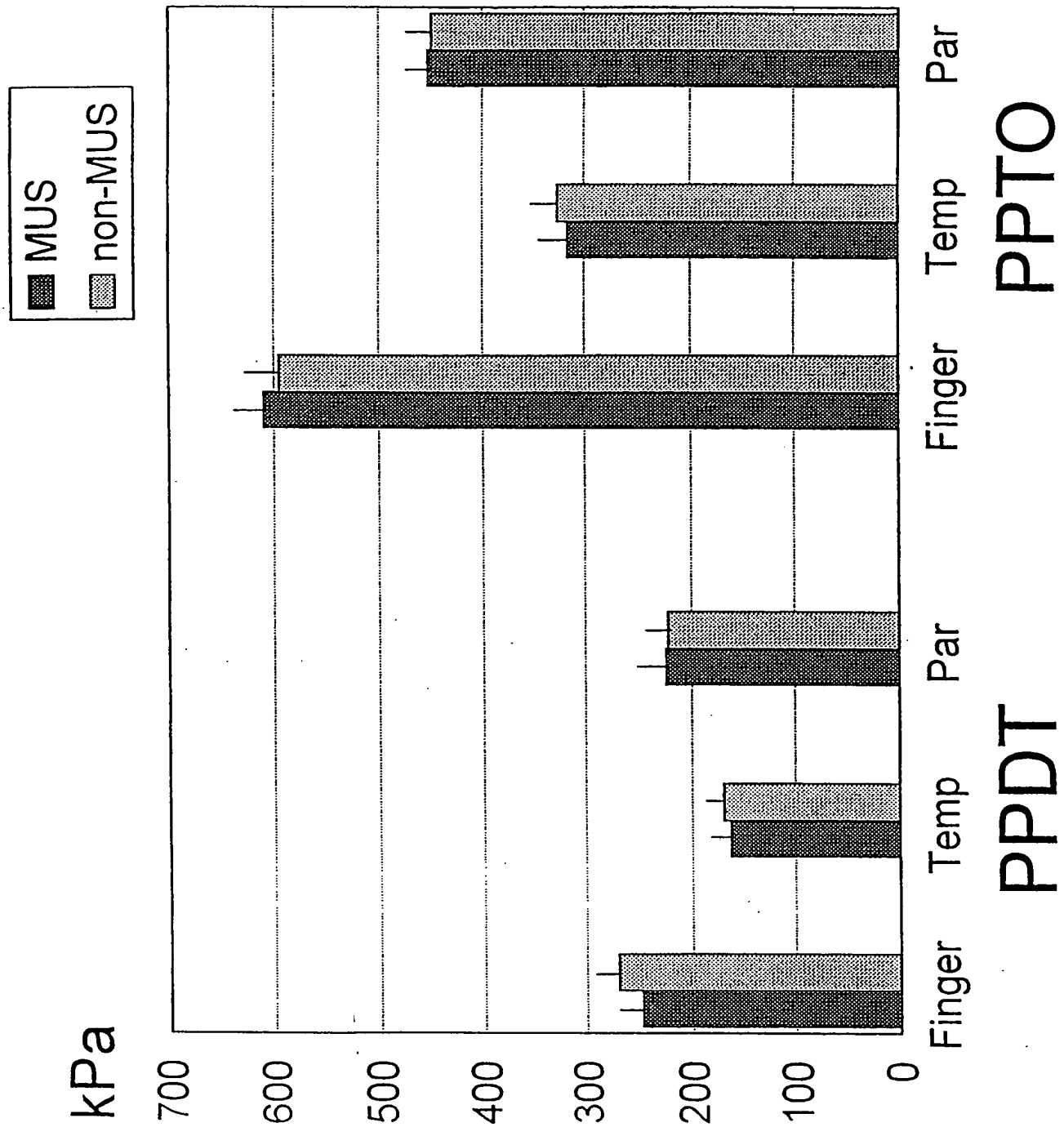


Fig. 17